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The journal has a goal of serving as an important resource material in diabetes for its readers, mainly in the developing world.

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EDITORIAL

Emerging health care technologies in diabetes: is it the way forward?

Rajeev Chawla[1]

Published online: 15 May 2023

The last almost 3 years have been a turning point of sorts for humankind. The COVID 19 pandemic stopped everything in its tracks and drastically changed almost all aspects of our lives. One such paradigm change has been in healthcare delivery, with technology coming to the rescue of many people whose only access to their healthcare providers was through different tech modalities -bringing telemedicine centre-stage. Doctor consultations changed from physical consultations in doctor clinics to audio-visual consultations in the virtual clinic bridging the physical distance, separating the two and bringing them face to face in a virtual world. Data shows a significant increase in use of telemedicine, not only in the developed world but also in the developing countries like India [1].

Telemedicine entails using telecommunication technology for remote diagnosis and treatment of patients. Information on the patient's health status is shared with the healthcare practitioner (HCP) using digital technologies (such as smart phones, computers, i-pads, and digital therapeutic pills). The HCP connects virtually with the patient for an audio-visual teleconsultation, assesses the health condition of the patient, and offers diagnosis and management advice. Hence, telemedicine has fast emerged as both a screening and diagnostic tool. Though telemedicine has been around for a longer time, but the pandemic brought it to the forefront as a practically viable option for many patients who were unable to step out of their homes for a physical visit to their HCP clinic. Data shows a huge increase in teleconsultations through digital platforms or devices, reducing the need for a physical visit to the doctor's clinic, minimising the risk of exposure for both parties involved, as well as saving time and cost- a win-win situation for both!

Technology today enables a better understanding of the patient's glycemic status using newer tools such as continuous glucose monitoring (CGM) that enable a customised management of their glycemic profiles. It helps to connect with patients virtually from the confines of their homes and to reach out to them as and when needed, without the need of a physical face-to-face visit and communicate with them through different digital platforms and tools. Technology also has helped taking health care to the doorstep of patients even in remote areas where delivery of specialised expert services had been a logistic and infrastructural nightmare earlier [1].

A study by Ritika Verma et al. in the current issue "Personalized glycemic response led digital therapeutics program improves time in range in a period of 14 days" [2] analysed data from continuous glucose monitoring (CGM) of 64 participants with T2DM. The CGM data was analysed for a period of 7 days, before and after the introduction of modified lifestyle plan. Primary outcome of the study was change in time in range (TIR) & secondary outcomes of the study were change in mean blood glucose, time above range (TAR), time below range (TBR), and glucose management indicator (GMI). Significant improvement in glycemic control was observed after the introduction of personalized lifestyle plan. Median reduction in mean blood glucose was from 139.5 mg/dL to 122 mg/Dl. TIR and GMI improved from 70.50 to 75.00% and 6.64 to 6.23% respectively. TAR reduced significantly from 17.00 to 6.00%

Another study by R Chawla et al. published in JMIR 2022 titled "Clinical Utility of a Digital Therapeutic Intervention in Indian Patients with Type 2 Diabetes Mellitus: A 12-week, prospective, single-arm, intervention study" [3] has shown Lifestyle modification through digital therapeutics brings HbA1c down, thereby bringing diabetes under control. In this study, a significant reduction in the HbA1c of 0.84%, in FBG of 8.39 mg/dl and in PPBG of 14.97 mg/dl was observed for the overall study population at the end of 12 weeks.

Study by Jia Zhang et al. published in current issue "Telemedicine with advanced communication technology in management of type 2 diabetes mellitus: A network meta-analysis" [4] included thirty-five studies consisting of 5029 type 2 diabetes mellitus patients and 4 interventions

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including computer-based self-management, telephone-based self-management,telemonitoring self-management, and usual care of clinic. In network meta-analysis, the computer-based self-management has the highest probability to be the most effective way in diabetes self-management treatments. It concluded that computer-based, telephone-based, and telemonitoring self-management methods are effective self-management methods for type 2 diabetes mellitus.

Study by Chawla et al. "Diabetes Care During COVID-19 Pandemic Using a Telehealth Approach" published in Endocrine Practice 2021 is a retrospective assessment of patients with diabetes, with and without COVID-19 infection, during the lockdown period managed through a dedicated comprehensive telehealth platform [5]. The virtual health applications comprised of telephone consultations and video telehealth consultations. We concluded that digital virtual diabetes clinic has a potential to provide efficient method of consultative service.

In the current issue study by Abhinav Bassi et al., "Innovative mobile- health led Participatory Approach to Comprehensive Screening and Treatment of Diabetes (IMPACT Diabetes) [6] evaluated a community-level technology-enabled system-level intervention based around the community health workers and primary-care physicians. This study suggests technology enabled transfer of simple clinical procedures from physicians to non-physician health workers can support the provision of healthcare in under-served communities. Community health workers can successfully screen and refer patients with diabetes and/or CVD to physicians in primary healthcare system.

Technology has been a gamechanger of sorts in the health care sector. Telemedicine, digital health platforms and tools, digital health solutions are fast gaining popularity and have changed the entire healthcare sector. We are fast adapting to the changing healthcare delivery scene and with more and more technological advancements it is anybody's guess on what the future may bring!

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REVIEW ARTICLE

A systematic review on foot muscle atrophy in patients with diabetes mellitus

Neerja Thukral[1] · Jaspreet Kaur[1] · Manoj Malik[1]

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Abstract

Introduction Skeletal muscles respond heterogenically under various stresses and conditions like diabetes mellitus and cancer. Various imaging techniques like radiographs, ultrasonography, and MRI have been used to find out the muscle mass and cross-sectional area of foot muscles.

Objective To summarize the findings of various imaging techniques to draw inference of presence of foot muscle atrophy in diabetic patients.

Methodology Articles from databases-PubMed, Science Direct, Taylor & Francis, and Springer Link were retrieved.

Results The imaging techniques confirm the presence of atrophy of foot muscles.

Conclusion Based on the findings of study, it can be concluded that foot muscle atrophy is present in diabetics, with intrinsic muscles affected first in terms of decreased cross-sectional area, reduced plantar tissue and skin thickness, and a decrease in total foot muscle volume.

Keywords Intrinsic foot muscle · Muscle atrophy · Diabetes mellitus · Systematic review

Introduction

Skeletal muscles account for 40% of total mass of the human body and are heterogeneous in structure and function. The muscle fibers that make up skeletal muscles are classified on the basis of their biological characteristics as well as functions [1]. This constitution of fibers in muscles is unsteady and responds via muscle fiber transition which is an important mechanism for muscular adaptation. When subjected to varying degrees of cellular stresses, these muscles respond heterogenically. However, the responses can be in the form of neural changes, vascular changes, ultra-structural changes, and/or muscle atrophy [1, 2].

Muscle atrophy is defined as a decline in the muscle mass. It can be either complete muscle wasting or partial [3]. There are various physiological as well as pathological conditions or insults that can lead to muscle atrophy, relatively common of which are ageing, prolonged disuse and chronic disease like Cancer, Diabetes Mellitus etc. [4]. Muscle atrophy results due to unconstructive balance between rate of contractile protein synthesis and degradation. The degradation of these contractile proteins is caused by ubiquitin-proteasome, autophagy-lysosome and caspase-3-mediated proteolytic pathways. Diabetes Mellitus is a condition in which the host cells are either resistant to insulin or deficient in insulin. In this condition, there occurs prolonged activity of the above mentioned pathways leading to an increase in degradation of contractile protein. The primary regulator of protein synthesis is the activation of mammalian target of rapamycin (mTOR), whict is activated by Akt (a serine /therokinase previously known as Protein Kinase B(PKB)) in skeletal muscle either by insulin or insulin like growth factor and mechanical stimulus. Akt also interacts with ubiquitinproteasome and autophagy lysosome pathways. Insulin resistance in diabetes mellitus causes reduced activation of Akt, which in turn decreases phosphorylation and reduces pro-inflammatory cytokines (IL-6, TNF-α) leading to attenuation of muscle atrophy signaling [4, 5].

Studies have reported that skeletal muscles in diabetes mellitus undergo atrophy leading to reduction in muscle mass [6]. Owing to continuous loss of motor axons, the most common complication of diabetes, i.e., neuropathy (motor) also results in muscle atrophy, which in combination with insufficient reinnervation results in denervation of muscle fibers

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resulting in structural deformities of foot [7, 8]. Atrophy is usually seen distally, i.e., in small muscles of hands, intrinsic foot muscles, anterior calf muscles usually tibialis anterior, which leads to foot deformities like equinus, hammer toe, and claw deformity [8–10]. Studies also suggest that deterioration of intrinsic foot muscles is preceded by deterioration of extensor digitorum longus as a sequel of distal to proximal neuropathy and attributes to metatarsophalangeal joint deformities [11, 12].

Since muscle atrophy is an indispensable part of diabetic neuropathy and is related to severity of neuropathy, foot muscle mass and volume as well as plantar tissue thickness can be detected easily in foot with the help of various imaging techniques. The techniques used for determining foot muscle volume in various studies are radiographs, ultrasonography, magnetic resonance imaging (MRI), nerve conduction studies, and computed tomography etc. [10, 12–24].

So, the current systematic review was conducted with an objective to summarize the findings of various imaging techniques in order to draw inference of muscle atrophy present in diabetic patients irrespective of presence or absence of neuropathy.

Methodology

Methods The present systematic review was designed and conducted in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [25] and was registered under International Prospective Register of Systematic Reviews (PROSPERO) (identification number CRD42021169173) (Fig. 1).

Search strategy Electronic databases — PubMed, Science Direct, DOAJ (Directory of Open Access Journals), Taylor Francis, and Springer Link — were searched from January 2000 to March 2020 with language restricted to English. The keywords used were as follows: "foot muscles," "foot muscle atrophy," "diabetes mellitus," combined with BOOLEAN operators. Synonyms of search terms were also used to expand the search. Studies that reported measurement of foot muscle mass, volume, and thickness of plantar tissues by using plain radiographs, ultrasonography (US), nerve conduction studies (NCS), and magnetic resonance imaging (MRI) were included in the study. Exclusion criteria included application of any exercise protocol or therapeutic intervention.

Duplicates were removed using Mendeley software and titles and abstracts were screened for inclusion criteria. Two investigators independently screened the titles and abstracts of the identified records. The studies meeting inclusion criteria were included and their full texts retrieved and examined. Any disagreements were resolved by consensus with a third investigator. Also, references of included studies were searched and examined. The quality check of included studies was done by CARS checklist [26]. Furthermore, bias of the studies included was removed by JBI critical appraisal checklist for diagnostic studies [27].

Results

The electronic database search yielded 1258 citations, out of which 11 fulfilled the selection criteria. Table 1 summarizes findings of included studies and Table 2 describes quality check of included studies by CARS checklist.

Table 3 determines risk of bias assessment of included studies and inferred that all the studies were to be included in the review.

Discussion

The results of this review show that the various imaging techniques used for detecting or measuring foot muscle mass and volume, its cross-sectional area, and/or plantar thickness in patients suffering from diabetes mellitus with or without neuropathy indeed confirm the presence of intrinsic foot muscleatrophy (Table 3). The various imaging techniques used are radiographs [12], magnetic resonance imaging [12–14, 21], ultrasonography [10, 17–20, 23, 24], and nerve conduction studies [20].

It is clinically important to detect atrophy of foot muscles in diabetics as the process is related to development of neuropathy and altered foot biomechanics, thereby leading to thinning of sub meta-tarsal fat pads and prominence of meta-tarsal heads, increasing the risk of foot ulcers and various foot deformities [16, 20, 21, 24].

Severinsen et al observed close relations between ultrasonography and neurophysiological findings when determining extensor digitorum muscle cross-sectional area and thickness of MIL muscles (muscles between 1st and 2nd meta-tarsal bone). Decreased amount of muscle at US was observed in patients with small CMAPs which can be due to dispersion of muscle fibers that are embedded in fibrous and fatty tissues [20]. Moreover, foot muscle volume as detected by MRI and ultrasonographic estimates of foot size were meticulously related, indicating presence of intrinsic foot muscle atrophy [23].

Kumar et al documented reduced thickness of adductor hallucis, interosseus muscles, and decreased cross-sectional area of extensor digitorum muscle in diabetics with high-frequency ultrasonography. Thickness of plantar skin and fascia was also found to be reduced. Glycosylation by non-enzymatic process may cause loosening of functional capability of the plantar fascia, intrinsic foot muscles, and ligaments

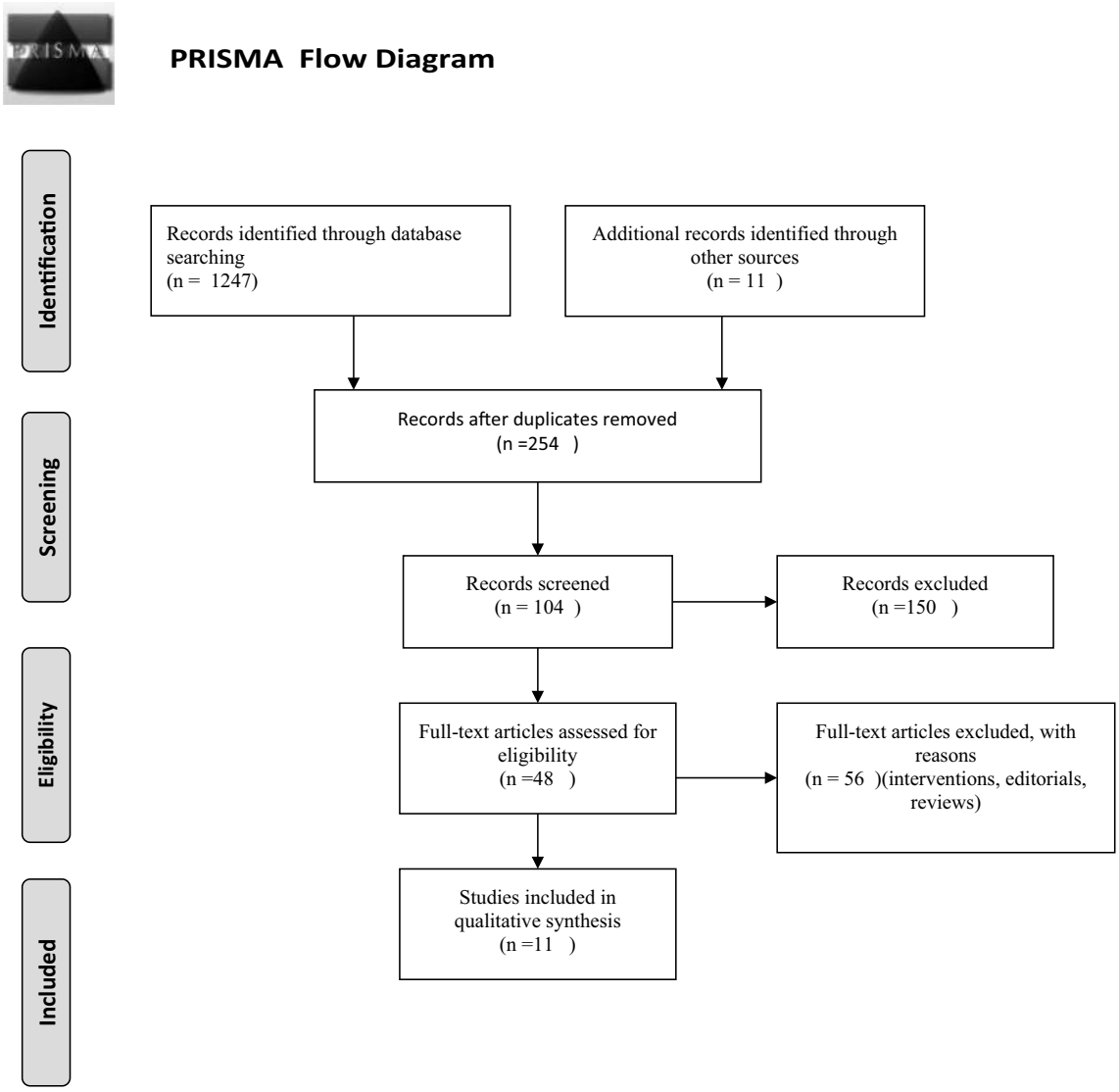

Fig. 1 PRISMA flow diagram for study selection

to control joint movement, thereby causing plantar tissue changes and muscle atrophy [10]. Chao et al also support the finding that with the progression of diabetes, epidermal thickness becomes thinner on plantar skin surface especially in neuropathy and ulceration while in diabetics without any foot complications or neuropathy, epidermal plantar skin is hyperplastic. This is thought to be the outcome of hyperglycemia induced advanced glycation products accumulation [19]. One study by Sun et al did not find any considerable differences in plantar soft tissue thickness between diabetics and controls. This could be due to altered testing position of supine with extended knees as compared to previous studies in which subjects were placed prone with flexed knees. Altered knee, ankle position may be the possible cause for changed plantar tissue thickness or tightness [17].

Muscle atrophy may also be caused due to pathological changes of metabolism involving complex cellular and molecular mechanisms, and of microvessels. The condition worsens with the presence of neuropathy and causes serious implications. Since high-frequency ultrasonography captures clear pictures of foot muscles in patients suffering from diabetics, it can detect foot muscle atrophy in later stages as well as early stages without neuropathy. In order to detect muscle atrophy early, extensor digitorum brevis muscle is considered the optimal group as it is the earliest muscle to shrink [24].

In addition to ultrasonography, MRI is also an effective imaging tool to detect muscle atrophy as is supported by several studies, as significant atrophy was found in foot muscles of diabetics when compared to controls [11–14, 21, 22]. MRI documented studies carried by Bus et al state that diabetic patients with neuropathy account for 73% reduced intrinsic foot muscles cross-sectional area [14]. Greenman et al found decreased thickness of foot muscles at level of meta-tarsal joints in neuropathic as well as non-neuropathic diabetics

Table 1 Characteristics and findings of included studies

Sr. No.	Author	Study location	No. of participants	Imaging technique used	Findings
1	Kumar CGS et al, 2015 [10]	Manipal, India	*N*=60 (30 type 2 diabetes mellitus (T2DM), 30 non-diabetes mellitus (NDM))	Plantar tissue, as well as intrinsic foot muscles thickness under metatarsals, was measured by high-frequency musculoskeletal ultrasonography	Thickness of plantar tissue and intrinsic foot muscles was found to be reduced substantially in patients with T2DM as compared with NDM
2	Cheuy VA et al, 2013 [12]	St. Louis, MO, USA	*N*=35 (23 diabetic, neuropathic subjects,12 controls)	Deterioration of intrinsic foot muscle and metatarsophalangeal joint angle was measured by radiographs and MRI. Physical performance evaluated by the Foot and Ankle Ability Measure	Muscle deterioration ratio was found to be higher and Foot and Ankle Ability Measure scores were lower in the diabetic neuropathic group
3	Andersen H et al, 2004 [13]	Denmark	*N*= 46 (23 long-term diabetics (15 neuropathic, 8 non-neuropathy), 23 healthy control)	Total volume of intrinsic foot measured through cross-sectional magnetic resonance images of non-dominant foot	In patients suffering from diabetes, foot muscle volume was found to be halved
4	Bus S A et al 2002 [14]	Pennsylvania	*N*=16 (8 diabetic polyneuropathy (DPN) patients, 8 healthy controls)	Multiple spin-echo MRI metatarsal regions of foot, frontal plane sections	Remarkable atrophy of intrinsic muscles in neuropathic subjects as compared to controls
5	Sun JH et al, 2011 [17]	Hong Kong	*N*=124 (70 DPN subjects, 54 healthy controls)	Tissue ultrasound palpation system to measure stiffness and thickness of plantar soft tissues over pulp of big toe, heel, and 1st and 2nd meta-tarsal head	People with diabetic polyneuropathy had stiff plantar tissues than healthy control
6	Hendersen AD et al, 2020 [18]	USA	*N*=30 (15 DPN, 15 matched controls)	Ultrasound imaging to measure size of 10 different lower leg and foot muscles	In individuals with DPN, only one (toe extensor) of the six extrinsic and four intrinsic foot muscles was found to be smaller in size
7	Chao CYL et al, 2011 [19]	Hong Kong	*N*=112 (72 diabetics (22 neuropathies, 16 foot ulcerations, 34 pure diabetics), 40 controls)	High-frequency ultrasonography and tissue palpation ultrasound system to determine epidermal layer thickness of plantar skin, thickness and stiffness of total plantar tissue at big toe, first, third, and fifth metatarsal heads, and the heel pad respectively	There was 15% reduction in epidermal plantar skin thickness in patients with diabetic foot ulceration and 9% in patients with neuropathy when compared to control group
8	Severinsen K et al, 2007 [20]	Denmark	*N*=26 (diabetics)	Amplitude and area of Compound Muscle Action Potential (CMAP), conduction velocity of peroneal and tibial nerve by electromyography on the non-dominant side. Cross-sectional area determined by ultrasound of (a) extensor digitorum brevis muscle (EDB) and (b) muscle group between first and second meta-tarsal bone (MIL)	Atrophy of EDB muscle closely reflected by CAMP with reduced nerve conduction velocity. Close relation was found between muscle size as obtained by US and neurophysiological findings
9	Greenman RL etal, 2005 [21]	Boston	*N*=33 (12 control, 9 non-neuropathies, 12 neuropathic diabetics)	MRI at 3 tesla to determine cross-sectional area of foot to muscle tissue ratio	The muscle/total area ratio was different among all the three groups with presence of small muscle atrophy in all diabetics
10	Severinsen K et al, 2007 [23]	Denmark	*N*= 52 (26 diabetics, 26 controls)	Ultrasonography to determine thickness and cross-sectional area of EDB and muscles of first interstitium	Atrophy of intrinsic muscles is present in diabetics and can be detected by ultrasonography
11	Wang X et al, 2014 [24]	China	*N*=156 (56 DPN, 50 without DPN, 50 healthy controls)	High-frequency ultrasonography to examine transverse diameter, thickness and cross-sectional area of EDB, and thickness of first interstitium muscles of non-dominant foot	Transverse diameter, thickness and cross-sectional area of EDB and thickness of first interstitium muscles were significantly smaller in patients with DPN and without DPN than control group

Table 2 Methodological quality assessment by CARS checklist

Sr. No.	Author	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Result
1	Kumar CGS et al, 2015 [10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
2	Cheuy VA et al, 2013 [12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
3	Andersen H et al, 2004 [13]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	High
4	Bus S A et al 2002 [14]	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Acceptable
5	Sun JH et al, 2011 [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
6	Hendersen AD et al, 2020 [18]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Acceptable
7	Chao CYL et al, 2011 [19]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	High
8	Severinsen K et al, 2007 [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
9	Greenman RL et al, 2005 [21]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High
10	Severinsen K et al, 2007 [23]	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Acceptable
11	Wang X et al, 2014 [24]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Acceptable

[21]. Also, a study by Andersen et al shows a decrease in foot muscle volume by half in diabetics with neuropathy.

A recent study by Henderson et al suggests that early-stage atrophy is principally restrained to intrinsic muscles of foot. Also, the findings suggest that muscle deterioration is first seen in hands and feet which is followed by forearm and lower leg, thereby progressing in distal to proximal pattern.

USG was first used in 1980 and 1991 to study muscles and nerves respectively, after which it has evolved as a valid technique to diagnose diseases respective to these two entities [28]. It is found to be a reliable measure with a correlation coefficient of 0.98 to 0.99 and correlation of 0.99 with MRI scan of a muscle. USG instruments are equipped with electronic calipers so as to identify and measure the boundaries of muscle once imaged [28–30]. The useful parameters used to study muscle via USG are muscle size and echogenicity. The healthy the muscle is, dark is its reflection, i.e., it is echolucent and if the muscle undergoes atrophy, necrosis, or any other diseased condition, the muscle becomes more echogenic due to set up of multiple new planes for sound reflection [28]. MRI on the other hand provides excellent soft-tissue contrast resolution and multiplanar tomographic display [31]. It shows areas where the muscle has been replaced by fat [32]. To assess muscle anatomy, detect fatty infiltration, which reflects remote damage and muscle loss, and crudely assess muscle volume for atrophy or hypertrophy, T-1 weighted images can be used [14].

Also, when the techniques used for detecting foot muscle atrophy in diabetic patients, it was found that high-frequency ultrasonography and magnetic resonance imaging scans (MRI) were found to be effective in detecting the aforementioned condition even before clinical symptoms set in, though ultrasonography was found to be superior than MRI scans as MRI scans are time consuming, expensive, and inconvenient for bed side examination [24, 28–31].

Thus, findings of this study suggest that muscle atrophy is present even in initial stages of the disease even in absence of

Table 3 Risk of bias assessment by JBI Critical Appraisal Checklist for Diagnostic Test Accuracy Studies

Sr. No.	Author	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Result
1	Kumar CGS et al, 2015 [10]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
2	Cheuy VA et al, 2013 [12]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
3	Andersen H et al, 2004 [13]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
4	Bus S A et al 2002 [14]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
5	Sun JH et al, 2011 [17]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
6	Hendersen AD et al, 2020 [18]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
7	Chao CYL et al, 2011 [19]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
8	Severinsen K et al, 2007 [20]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
9	Greenman RL et al, 2005[21]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
10	Severinsen K et al, 2007 [23]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
11	Wang X et al, 2014 [24]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include

neuropathy. With the progression of disease and onset of neuropathy atrophy is further accentuated with altered biomechanics and deranged structure and function of foot, thereby leading to foot deformities, ulceration, and plantar pressure abnormalities. Thus, early detection of atrophy should be carried out via imaging techniques in order to manage the condition accordingly.

Clinical implications

Findings of this review suggest that muscle atrophy is indeed a feature of diabetes and is present irrespective of presence or absence of neuropathy in diabetic population, which can be a probable reason for balance and postural impairments in the same population. Therefore, measures should be taken for improving or maintaining muscle mass and volume in order to avoid various deformities that result due to underlying atrophy.

Conclusion

Depending on the results of study, it can be deduced that foot muscle atrophy is present in diabetics, with intrinsic muscles affected first in terms of decreased cross-sectional area, reduced plantar tissue and skin thickness, and a decrease in total foot muscle volume.

Although studies have shown that muscle atrophy leads to decreased muscle strength as well as sensitivity, which can further lead to locomotor impairments like reduction in gait velocity, altered muscle activity, changed kinematic pattern of lower limb in patients with diabetes mellitus, and diabetic neuropathy, this study did not address such impairments. So in future studies, overall impact of muscle atrophy on gait and locomotor disturbances, postural and balance impairments can be addressed.

Declarations

Conflict of interest The authors declare no competing interests.

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REVIEW ARTICLE

Telemedicine with advanced communication technology in management of type 2 diabetes mellitus: a network meta-analysis

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Abstract

Background Type 2 diabetes mellitus has risen to one of the most common chronic diseases worldwide, which puts heavy pressure on patients and the health-care system. Self-management is an important treatment for type 2 diabetes. New self-management treatments have been making great progress with the development of the advanced telemedicine.

Objective The purpose of this study is to gauge and examine the blood glucose control of various self-management strategies through a network meta-analysis.

Methods We search the articles through PubMed, Cochrane library, MEDLINE, and EMBASE databases to seek out randomized controlled trials, and the primary outcome was the change in HbA1c from baseline. This meta-analysis was conducted to compare different kinds of self-management methods, applying Revman 5.3, Stata 14.0 software, and GeMTC 0.14.3.

Results Thirty-five studies were included, consisting of 5554 type 2 diabetes mellitus patients and 4 interventions including computer-based self-management, telephone-based self-management, telemonitoring self-management, and usual care of clinic. In addition to performance bias, the risk of bias of included studies was low. In network meta-analysis, the computer-based self-management has the highest probability to be the most effective way in diabetes self-management treatments.

Conclusion In conclusion, computer-based, telephone-based, and telemonitoring self-management methods are effective self-management methods for type 2 diabetes mellitus. The computer-based self-management method was the most effective compared to the other two self-management methods.

Clinical trial registration The detailed protocol was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO). Registration number was CRD42020186839.

Keywords Type 2 diabetes mellitus · Self-management · Computer · Telephone · Nurse

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disease in the world, which is characterized by high incidence of complications, especially in developing countries. It is estimated that the global population with type 2 diabetes will exceed 9% in 2035 [1]. As the UKPDS mentions, the greater the population of type 2 diabetes in the world, the greater the pressure and burden on patients and health systems will be [2, 3]. Diabetes can cause a variety of complications, majorly including myocardial infarction, stroke, diabetic peripheral neuropathy, diabetic retinopathy, diabetic nephropathy, and diabetic autonomic neuropathy. These complications are common in patients with poor glycemic control, leading to higher rates of disability and mortality in this population. Diabetes self-management education and support (DSMES) provides diabetic patients with sustainable assistance, which mainly includes information and knowledge of diabetes to encourage patients' autonomy to self-manage their diabetes. The DEMES, consisting of education and support for patient self-management, is a management approach that improves health outcomes and the quality of life. According to previous studies, self-management not only plays an important role in blood glucose control, but also can prevent and delay the

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occurrence of diabetes-related complications. What's more, self-management is an important treatment for type 2 diabetes clinically. The support for self-management of diabetes is mainly provided through the daily care and clinical daily care of diabetic patients, which can help diabetic patients from the aspects of clinical problems, educational problems, social psychological problems, and behavioral problems. Due to a lack or delay in communication between patients and health care providers in usual nursing, the achievement of the blood glucose control target was far from satisfactory with the support of patient's health care team [4].

In recent years, with the development of medical care technology, self-management has been greatly developed. New self-management methods emerge in an endless stream, including the computer, mobile phone, mobile health, artificial intelligence, telemedicine, and other technologies [1, 2, 5]. As the examples of previous studies show, through these virtual diabetes care, a large amount of data from the diabetes patients can be collected and processed, such as vital signs, symptoms, and blood glucose. These specific technologies can facilitate the communication, examination, and treatment redirection, which enables the appropriate clinical decision to be made according to individual conditions. As the American Association of Diabetes Educators recommends, these interventions can enhance diabetes education, improve compliance, improve metabolic control, and raise the management efficiency of diabetes [6–8] .

However, the effects of these self-management studies were examined by direct comparison studies or traditional meta-analyses. As far as we know, traditional meta-analysis evaluates only a single intervention which makes clinicians confused when choosing a reasonable self-management plan. Based on the previous randomized controlled trials of self-management, the network meta-analysis was designed to comprehensively value the various self-management for T2DM in the present study [9].

Method

Protocol and registration

The elaborated protocol was registered in website of PROSPERO. Registration number was CRD42020186839. Our meta-analysis was consistent with the PRISMA statement and also the network meta-analysis extension statement of PRISMA.

Literature search

PubMed, Cochrane library, MEDLINE, and EMBASE databases (inception–2nd May, 2020) were used for retrieval, with "Type 2 diabetes mellitus" and "Self-management intervention" as key words. The search criteria were randomized controlled trials (RCTs) and reported in English language. The search strategies in details were displayed in supplementary file 1.

Inclusion criteria and exclusion criteria

The inclusion criteria used for selection of studies were listed as follows: (1) the patients of type 2 diabetes mellitus; (2) self-management interventions were based on advanced technologies, including computer-based interventions, APPs, telemedicine, mobile health and so on; (3) the main outcome was the change in HbA1c from baseline; (4) studies were limited to randomized controlled trials (RCTs). We excluded studies that met any of the following criteria: (1) non-randomly control trial was excluded, including cohort study, case-control study, case reports, case series, and narrative reviews; (2) cluster randomly control trial; (3) publications in non-English languages; (4) publications that did not provide sufficient data; (5) type 1 diabetes mellitus and pregnant diabetes; (6) animal experiments. Considering that there may be multiple papers published in the overlapping cohort, the latest results with the largest sample size will be selected for statistical analysis in this study.

Selection of studies

During the primary screening process, two reviewers independently screened the citation titles and abstracts to reserve relevant studies and examined each potential study through the full text individually in the secondary screening. Subsequently, the other two reviewers evaluated all relevant studies based on the inclusion and exclusion criteria. If there was any contradiction, the third author would be consulted on the solutions.

Assessment of study quality and data extraction

The risk of bias in the included studies was assessed using the Cochrane risk bias instrument which is commonly used tool in RCT quality assessment (the section that is being explained in detail of Cochrane was deleted).

This study extracted the following information and data from the included articles, mainly including the name of the author, the year of article publication, sample size, specific self-management, and HbA1c.

Two reviewers finished the quality assessment and data extraction. If there was any contradiction, the third author would be consulted on solutions.

Statistical analysis

We performed the pairwise meta-analysis and Bayesian NMA to investigate the efficacy of self-management in patients with T2DM, applying Revman 5.3 (Cochrane Collaboration, Oxford, UK), Stata 14.0 software (StataCorp LP, College Station, TX, USA), and GeMTC 0.14.3 (MRC Biostatistics Unit, Cambridge, UK). Standardized mean difference (SMD) with 95% confidence interval (CI) was calculated and reported to assess the efficacy of competing self-management methods for T2DM. Each self-management measure was carried out through the traditional pairwise meta-analysis of random effects [9]. The Bayesian model was used to sort the included measures, running 50,000 iterations for each of 4 chains, of which the first 20,000 iterations were used as burn-in. The surface under the cumulative ranking curve (SUCRA) was performed to evaluate the blood glucose control of the self-management for T2DM. We adopted the split-node method to check the existence of inconsistency [4]. Funnel charts were drawn to investigate the potential publication bias among the included studies [10].

Result

Selection of studies and characteristics of included studies

After removing duplicate studies, we preliminarily screened out 1349 original studies from the initial online search, of which 95 studies met the titles and abstract criteria. We subsequently read and evaluated the full text of these articles, and 60 of them were excluded for the following reasons: (1) repeated publication (*N*=2); (2) without valid data (*N*=45); (3) non-randomly control trial (*N*=4); (4) cluster randomly control trial (*N*=9). Finally, the remaining 35 studies were included in the current network meta-analysis according to the inclusion and exclusion criteria. The flowchart of the literature screening process was shown in Fig. 1. Table 1 summarized the characteristics of the included literature in this study

Methodological quality

Different self-management methods were not disguised as the same name, so that the participants were aware of their group after assigning tasks. According to the Cochrane risk of bias instrument, the included studies were judged to have high risk of performance bias due to the lack of blinding among personnel and participants. Further ambiguous risk biases were found through large proportion of studies within the domains of selection bias, including 16 of 35 studies (46%) in random sequence generation and 22 of 35 studies (63%) in allocation concealment. About 29 (83%) of 35 studies were assessed as having an unclear risk of detection bias. Additionally, all studies had ambiguous risk of bias in other. All studies have low risk of attrition bias, and 34 of 35 studies (97%) were considered as low risk of reporting bias. As shown in supplementary file 2, the final quality of the included studies indicated the relatively low risk of bias, which provided credible evidence for the outcome of meta-analysis.

Comparison of glycemic management

Thirty-five studies [6, 11–44] were included for data, consisting of 5554 T2DM patients and 4 interventions including computer-based self-management, telephone-based self-management, telemonitoring self-management, and usual care of clinic. The weighted network was presented in Fig. 2. The standardized mean difference (SMD) was used to evaluate the difference of blood glucose control effect of different self-management intervention methods. For the results obtained from the random effects standard deviation analysis, the consistency model of 0.33 (0.23, 0.49) was like the inconsistency model of 0.32 (0.21, 0.47), and the inconsistency standard deviation was 0.66 (0.03, 1.64). What's more, through the node-splitting analysis of Bayesian framework, there was a good consistency between direct comparison and indirect comparison in most of the included studies. The result of node-splitting analysis was presented in supplementary file 3. In traditional meta-analysis, statistical significance of traditional pairwise comparison was found in computer-based self-management of −0.53 (−0.71, −0.34) versus usual care, telemonitoring self-management of -0.25 (−0.43, −0.06) versus usual care, and telephone-based self-management of −0.42 (−0.52, −0.31) versus usual care. The differences in the efficacy of self-management interventions on blood glucose control were evaluated by network meta-analysis of Bayesian framework, as shown in Table 2. And the rank of the efficacy was presented in Fig. 3. According to Surface Under the Cumulative Ranking (SUCRA) shown in Table 3, the computer-based self-management method ranks first in the blood glucose control of patients with type 2 diabetes. As shown in Fig. 4 for comparison-adjusted funnel plot, the funnel graph illustrated that publication bias existed in the included studies, but the risk of publication bias could be considered low.

Discussion

To our knowledge, this was the first study to apply network meta-analysis to comprehensively evaluate the blood glucose control of different self-management interventions for patients with T2DM. We found that computer-based self-management, telephone-based self-management, and telemonitoring self-management were stronger blood glucose control than

Table 1 Characteristics of studies selected for meta-analyses

Study description					HbA1c reduction			
					Treatment group		Control group	
Source	Study location	Length of follow-up	Intervention	*N* (total)	Mean (SD)	*n*	Mean (SD)	*n*
Cho2006 [11]	Korea	30 months	Computer vs. usual care	80	−1 (1.308)	40	−0.1 (1.3)	40
Dario2017 [6]	Italy and Belgium	12 months	Telemonitoring vs. usual care	246	−0.26 (0.92)	168	−0.27 (0.99)	78
Döbler2018 [12]	German	12 months	Telephone vs. usual care	199	−0.68 (1.4)	98	0.12 (1.7)	101
Faridi2008 [13]	USA	3 months	Telephone vs. usual care	30	−0.1 (0.3)	15	0.3 (1)	15
Fortmann2017 [14]	Canada	6 months	Telephone vs. usual care	126	−1 (1.2)	63	−0.2 (1.778)	63
Kleinman2017	India	6 months	Telephone vs. usual care	90	−1.5 (1.1)	44	−0.8 (1.6)	46
Mcmahon2012 [16]	USA	12 months	Computer vs. telephone	102	−1.3 (1.4)	51	−1.5 (1.6)	51
Pressman2014 [17]	USA	6 months	Telemonitoring vs. usual care	225	−2 (1.8)	118	−1.8 (1.7)	107
Sun2019 [18]	China	6 months	Telephone vs. usual care	91	−1 (0.745)	44	−0.66 (0.781)	47
Tang2013 [19]	USA	12 months	Computer vs. usual care	415	−1.14 (1.637)	202	−0.95(1.776)	213
Stone2010 [20]	USA	6 months	Telemonitoring vs telephone	137	−1.7 (1.442)	64	−0.8 (1.353)	73
Vinitha2019 [21]	India	24 months	Telephone vs. usual care	248	−2.1 (1.873)	126	−1.7 (1.735)	122
Wang2019 [22]	China	6 months	Telephone vs. usual care	120	−1.5 (2.188)	60	−0.76 (2.207)	60
Wild2016 [23]	UK	9 months	Telemonitoring vs. usual care	285	−1 (1.353)	146	−0.4 (1.212)	139
Yoo2009 [24]	Korea	3 months	Telephone vs. usual care.	111	−0.5 (0.854)	57	0.2 (0.954)	54
Zhou2014 [25]	China	3 months	Computer vs. usual care	108	−1.6 (1.428)	53	−0.62 (1.575)	55
Cho2017 [26]	Korea	6 months	Telemonitoring vs. usual care	484	−0.31 (0.7)	244	−0.11 (0.76)	240
Hansel2017 [27]	France	4 months	Computer vs. usual care	120	−0.3 (0.94)	60	0.21 (0.7)	60
Jeong2018 [28]	Korea	24 weeks	Computer vs. telemonitoring	338	−0.81 (1.05)	112	−0.66 (1.09)	113
Jeong2018 [28]	Korea	24 weeks	Computer vs. usual care	338	−0.81 (1.05)	112	−0.66 (1.03)	113
Kwon2004 [29]	Korea	12 weeks	Computer vs. usual care	110	−0.65 (1.257)	55	0.43 (1.067)	55
Avdal2011 [30]	Turkey	6 months	Computer vs. usual care	122	−0.512 (0.875)	61	0.048 (1.08)	61
Cho2011 [31]	Korea	12 weeks	Compute vs. usual care	71	−0.5 (0.854)	36	−0.2 (1.054)	35
Duruturk2019 [32]	Turkey	6 weeks	Computer vs. usual care	44	−1.21 (1.277)	23	0.35 (2.478)	21
Kim2006 [33]	Korea	12 weeks	Computer vs. usual care	51	−0.59 (0.61)	28	0.43 (0.81)	23
Kim2016 [34]	China	5 months	Computer vs. usual care	182	−1.2 (0.7)	92	−0.6 (1.136)	90
Nicolucci2015 [35]	Italy	12 months	Telemonitoring vs. usual care	302	−0.5 (0.917)	153	−0.21 (0.985)	149
Crowley2016 [36]	USA	6 months	Telephone vs. usual care	50	−1.30 (1.685)	25	−0.3 (1.685)	25
Davis RM2010 [44]	USA	12 months	Telephone vs. usual care	165	−1.2 (3.324)	85	−0.2 (3.225)	80
Kempf2017 [37]	Germany	12 weeks	Telemonitoring vs. usual care	167	−1.1 (1.2)	93	−0.2 (0.8)	74
Anzaldo-Campos2016 [38]	Mexico	10 months	Telephone vs. usual care	202	−3.02 (2.83)	102	−1.3 (3.29)	100
Bujnowska-fedak2011 [39]	Poland	6 months	Computer vs. usual care	95	−0.26 (1.418)	47	−0.18 (1.576)	48
Wakefield2014 [40]	USA	12 weeks	Telemonitoring vs. usual care	94	0.1 (1.314)	41	0 (1.276)	53
Xu2019 [41]	USA	6months	Telephone vs. usual care	37	−0.69 (1.482)	19	−0.03 (1.744)	18
Yu2019 [42]	China	24 weeks	Telephone vs. usual care	95	−1.1 (0.3)	48	−1.1 (0.4)	47
Wang2019 [43]	China	6months	Computer vs. usual care	212	−1.1 (0.7)	106	−0.6 (1.136)	106

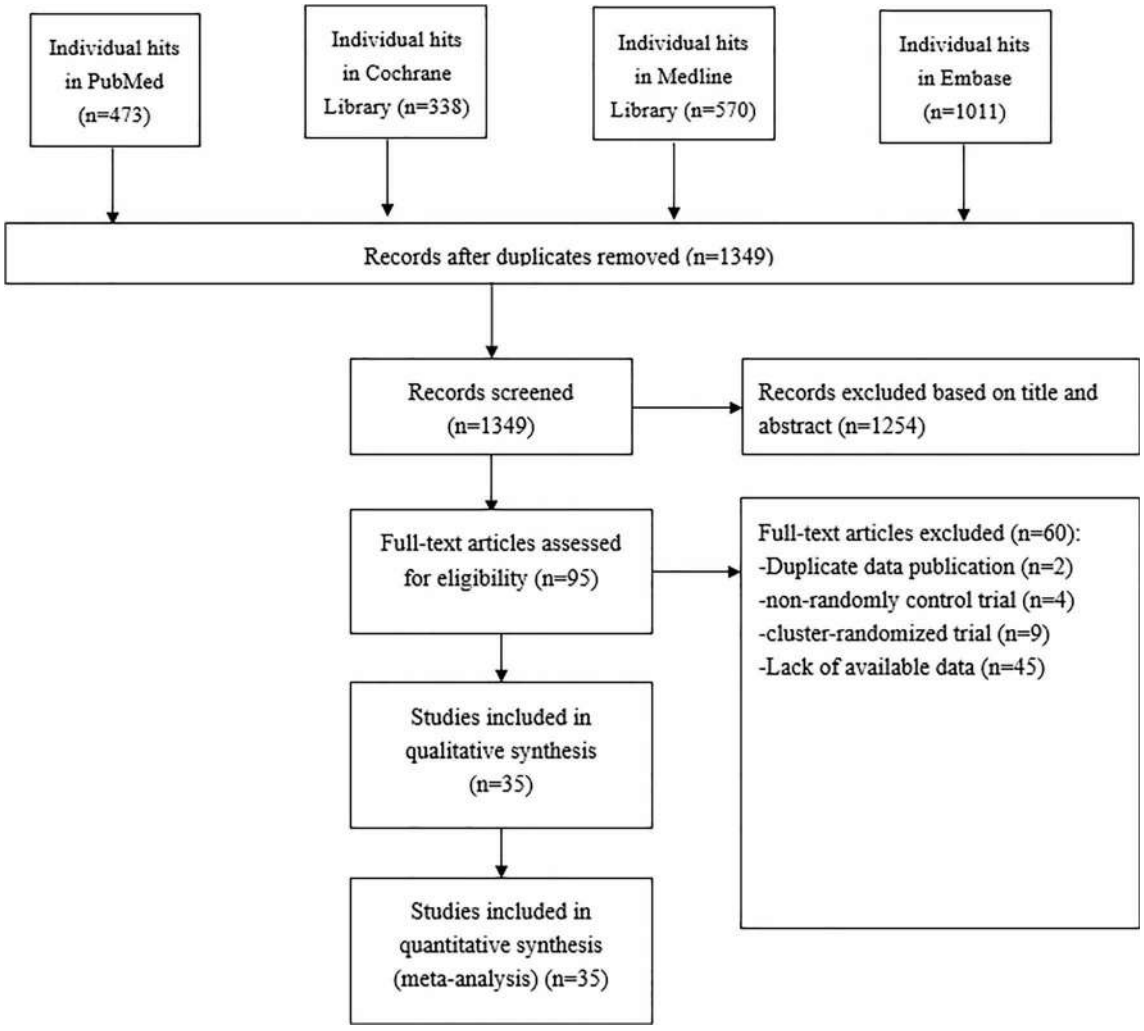

Fig. 1 PRISMA flow diagram

placebo in blood glucose management, and computer-based method was the strongest blood glucose control self-management method among them.

As far as we know, the network meta-analysis can provide the most comprehensive data analysis for advanced self-managements of T2DM patients. In our network meta-

Table 2 Comparisons of different categories of self-management

Standardized mean difference using traditional pairwise meta-analysis				
Standardized mean difference with network meta-analysis	computer	-	-	**-0.53 (-0.71, -0.34)**
	-0.18 (-0.52, 0.14)	telemonitoring	-	**-0.25 (-0.43, -0.06)**
	-0.04 (-0.35, 0.27)	0.14 (-0.18, 0.47)	telephone	**-0.42 (-0.52, -0.31)**
	-0.58 (-0.80, -0.36)	**-0.4 (-0.65, -0.15)**	**-0.54 (-0.78, -0.31)**	usual-care

The row and column values in the matrix represent the difference between the standardized averages of different self-management intervention. The statistics are expressed as standardized mean difference SMD (lower 95%CI, upper 95%CI). Statistically significant SMDS are highlighted in bold

Table 3 Surface under the cumulative ranking (SUCRA)

Intervention	SUCRA	PrBest	MeanRank
Computer	91.9	80.0	1.2
Telemonitoring	51.0	7.7	2.5
Telephone	57.1	12.3	2.3
Usual care	0.0	0.0	4.0

analysis, the included studies were tested using different methods. The percentage of changes of glycosylated hemoglobin before and after self-management was evaluated by SMD method. The evidence of meta-analysis was obtained from direct and indirect comparison tests. According to the node-splitting analysis of Bayesian framework, only 9 studies [6, 17, 20, 23, 26, 28, 35, 37, 40] showed statistical significance in direct and indirect comparison in telemonitoring self-management. The random effects standard deviation of both consistency model and inconsistency were similar in our network meta-analysis [45]. What's more, there was a difference between the random effects standard deviation and inconsistency standard deviation in inconsistent examination. In general, these examinations demonstrated good consistency in the included studies, so the data can be pooled for network meta-analysis. According to the SUCRAs and comprehensive ranking, computer-based self-management, telephone-based self-management, and telemonitoring self-management displayed substantial effects on blood glucose control of patients with T2DM. The result of our network meta-analysis was consistent with previous studies [1, 2].

As the abovementioned effective test of self-management showed, what these different self-management methods had in common was the use of advanced technology. The computer-based self-management, telephone-based self-management, and telemonitoring self-management involved several aspects of achieving blood glucose goals, including glycemic telemonitoring, physical activity, diabetes self-management education, and compliance [19, 22, 23]. All advanced self-management interventions can provide patients with a convenient way, which enables patients to get immediate assistance and make personalized blood glucose control programs at any time. Meanwhile, due to the infrequent or delayed contact between patients and health providers in usual care, patients might miss the best time for treatment [36]. Therefore, advanced self-management treatments might play an important part in the outcome that the computer-based self-management, telephone-based self-management, and telemonitoring self-management were more effective than usual care in glycemic control.

As the third strongest blood glucose control self-management in our network meta-analysis, the telemonitoring self-management used advanced technology to load data into the remote center of the health care provider through a personal modem. But there was usually a fixed time during which the health care provider processed patient data on a regular basis. Patients must wait for a reply from the health provider and there was a lack of direct contact between the patient and

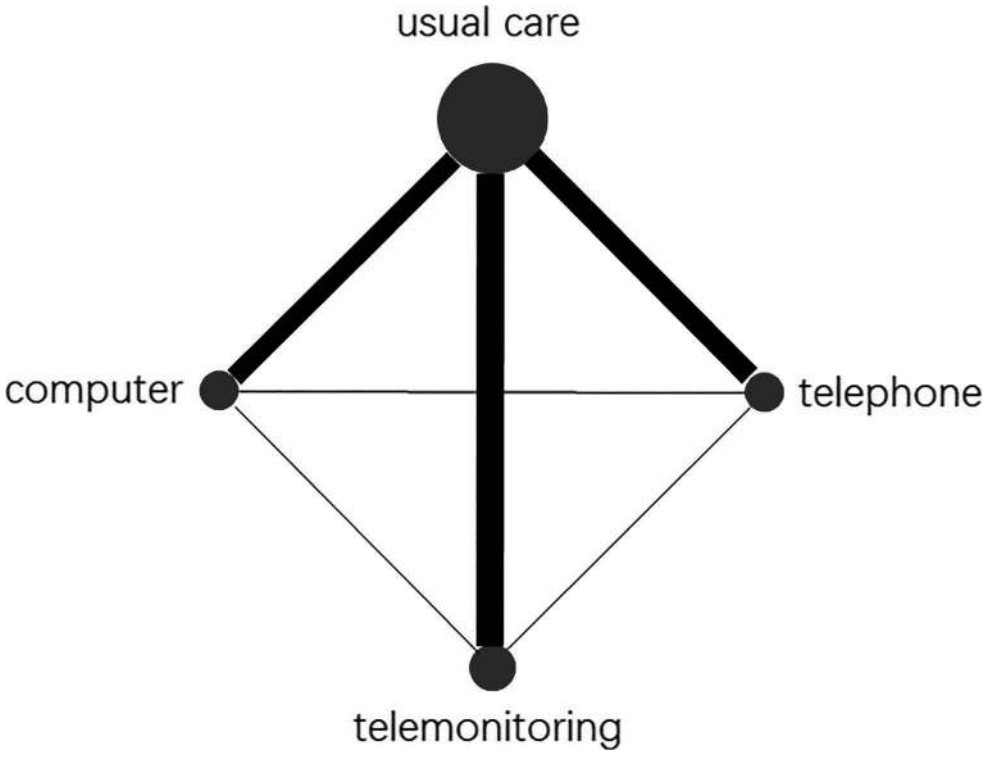

Fig. 2 Risk of bias summary: reviewers' judgments for each included trial about each risk of bias item

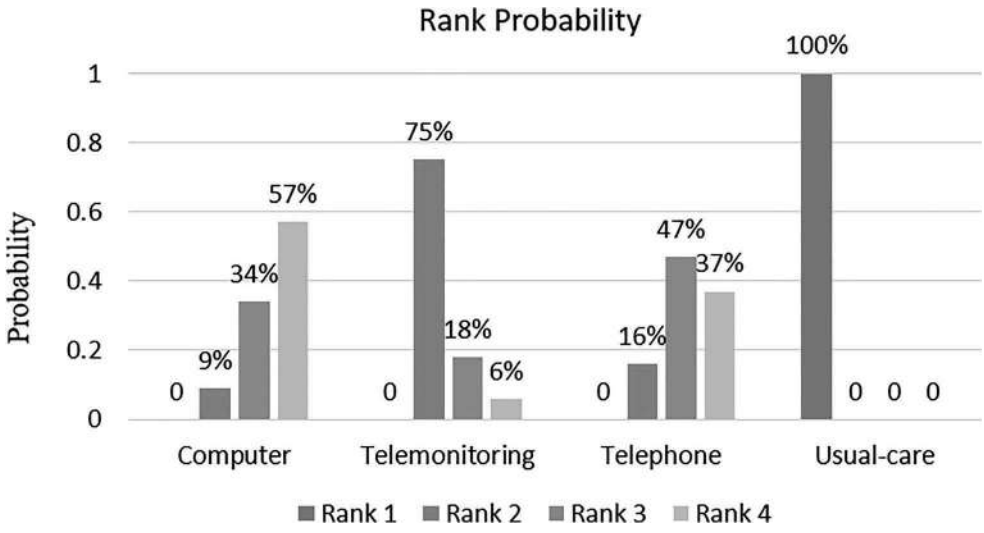

Fig. 3 Diagrams of rank analysis of efficacy comparisons

the provider. Besides, some of telemonitoring self-management still used clinical way to provide patient–provider contact [23, 26, 31]. Therefore, the blood glucose control of telemonitoring self-management was poorer than the computer-based self-management and telephone-based self-management.

For the included telephone-based self-management research, part of the research used mobile applications [18, 22, 46], and the other part of those research was based on the telephone communication and short message service [12, 21]. Providing counseling to patients through telephone communication and short message service can increase the enthusiasm of patients, while mobile applications or Internet software can provide complete guidance [16, 34]. And all of the computer-based self-management studies established a complete glycemic management system through the diabetes guidelines. Therefore, the computer-based self-management might be more effective in glycemic control than telephone-based self-management, which was consistent with the result of our network meta-analysis.

Although computer-based self-management was the most effective approach, there were still some advantages in other self-managements. With the development of technology, advanced self-management was no longer restricted by its own characteristics. For example, the telemonitoring device can provide communication function [26], and the smartphones

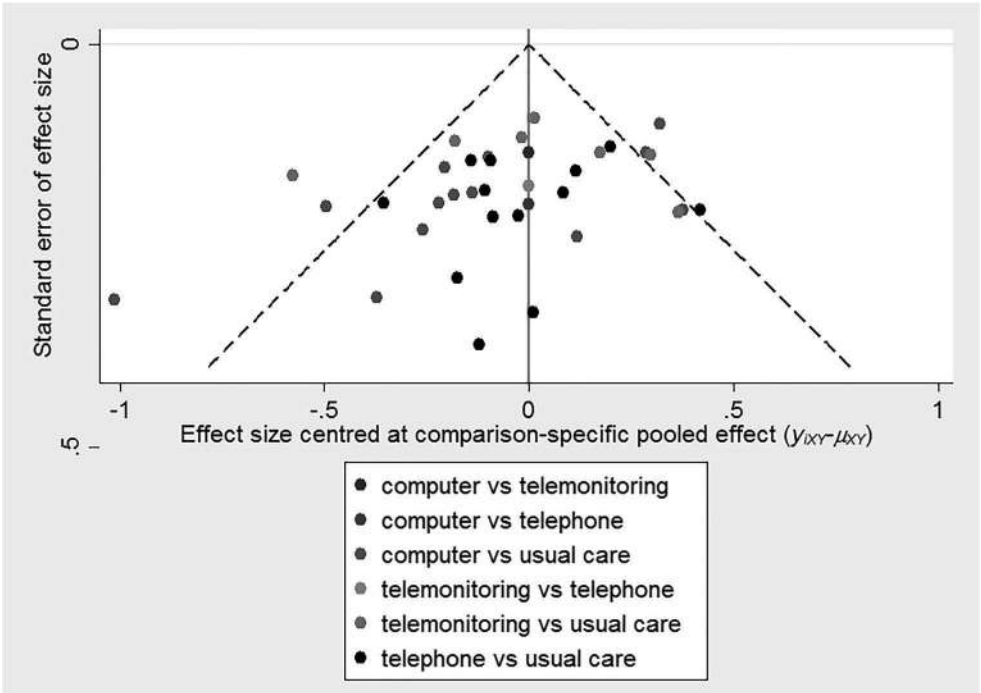

Fig. 4 The comparison-adjusted funnel plot

can provide full-featured mobile applications for T2DM patients through Internet services [18, 22]. The use of computers for self-management has not only been proved to be effective in controlling blood glucose, but its portability has gradually emerged with the popularity of tablet computers and laptops [47]. In the future, the treatment of diabetes will no longer rely on one type of self-management. It will use a variety of advanced self-management methods to achieve glycemic goals.

The limitations of our network meta-analysis were listed as follows: (1) Due to the inconsistency, the results of network meta-analysis might cause deviation; (2) only studies published in English were evaluated; (3) in the case of publication bias, some trials with negative results may not be published, so the evaluation may be biased; (4) the performers and participants were not blinded in all of the included studies so that the outcome of RCT might be impacted by artificiality; (5) lack of head-to-head trial of self-management methods.

Conclusion

The computer-based self-management was preferable to other self-management methods for T2DM. Compared to the other two self-management methods, the computer-based self-management method was the most effective. The effective self-management may be based on the strong functions of the computer. With the development of advanced technology, mHealth, or other convenient technology containing computer functions will be the potential way to the diabetes self-management in the future. More head-to-head studies with larger sample size and longer trial period are warranted to support our findings and explore the efficacy of advanced self-management treatments. In the future research, the cost of different self-management methods should also be regarded as one of the influencing factors of effectiveness evaluation.

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Declarations

Conflict of interest and Source of Funding None

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ORIGINAL ARTICLE

Pattern of clinical/bacteriological profile and follow-up of symptomatic urinary tract infection in patients with diabetes: a cross-sectional study from North India

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Abstract

Background and aims Diabetes patients have a higher risk of urinary tract infection (UTI). The present study was aimed at determining the clinical profile, microbial pattern, antibiotic sensitivity, and follow-up of UTI in patients with type 2 diabetes (T2D).

Materials and methods Two hundred consecutive T2D patients admitted with a diagnosis of UTI were selected for this study. Midstream urine specimens were collected and the culture tests were done by a quantitative method; antimicrobial sensitivity was determined by using the Kirby-Bauer method. After discharge from the hospital, patients were followed for 6 months.

Results Women (n=162) outnumbered men (n=38), with 76% being postmenopausal. Pyelonephritis was present in 44.5% (n=89) and emphysematous pyelonephritis (EPN) in 9.5% (n=19). Longer duration of diabetes, high body mass index, and prior UTI were risk factors for symptomatic UTI. Gram-negative bacilli were leading causes of UTI, with *E. coli* being the most common pathogen. Gram-negative pathogens were mostly sensitive to amikacin, imipenem, and piperacillin/tazobactam. Around 40% patients had recurrent UTI. The presence of renal calculi, poor glycemic control, and chronic kidney disease were significant predictive factors for recurrence.

Conclusion In patients with T2D, UTI was more common and severe in postmenopausal women. More than one-third of patients had a recurrence of UTI on follow-up for 6 months.

Keywords Type 2 diabetes · Urinary tract infection · Emphysematous pyelonephritis · Antimicrobial sensitivity

Introduction

People with diabetes are predisposed to many infections, urinary infections being the common ones [1–3]. Though UTI is common in women with diabetes, complications because of UTI are more often seen in men [4, 5]. UTI may present as mild disease at one end of the spectrum to pyelonephritis, septicemia, and acute kidney injury at the other end [6, 7]. Apart from bacterial, fungal infections are also common in these patients [8]. Diagnosis and determining the extent of the disease is often required with the help of radiology and microbiological testing. Proper identification of causative pathogen and institution of antibiotics as per culture and sensitivity is essential in addition to correction of fluid and insulin imbalance [9]. Widespread practice of self-treating with over the counter antibiotics is an important factor responsible for growing antibiotic resistance in UTI [10]. Proper microbiological studies are an important step at delaying the emergence of such bacterial resistance. Moreover, not many studies are available on follow-up of patients with symptomatic UTI especially with regard to recurrence and its adverse effect on kidney function [11]. Keeping the above facts in mind, the present study was aimed at documenting clinical and bacteriological profile as well as follow-up of patients admitted with symptomatic UTI at a tertiary care center in North India.

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Materials and methods

Patient population

This study was conducted in the departments of Endocrinology and Microbiology at a tertiary care hospital in North India. The study comprised of two hundred (200) consecutive patients of T2D admitted with symptomatic UTI and followed for 6 months after discharge from the hospital. All patients were examined at the time of admission with emphasis on particulars like age, duration of diabetes, marital and menopausal status in women, history of UTI and its treatment in the past, symptoms of present UTI like fever, dysuria, hematuria, frequency of urination, nausea/vomiting, flank pain, renal angle pain and altered sensorium. A detailed physical examination of the patients was carried out. Patients with recent hospitalization or surgery, use of antimicrobial drugs within the previous 2 weeks, patients on prophylaxis for recurrent UTI and history of recent urinary instrumentation were not included in the study. Similarly, patients with type 1 diabetes, gestational diabetes, or immunocompromised states (like HIV, malignancy, steroid intake, and transplant recipients) were also excluded from the study.

Investigations

Fasting and 2-h postprandial blood glucose (FPG and PPG respectively), serum urea and creatinine, 24-h urinary protein, and HbA1c were measured. The renal status of each patient was assessed using estimated GFR (eGFR), calculated from Modification of Diet in Renal Disease Study (MDRD) equation [12]. Plasma glucose concentration was measured by an enzymatic method using glucose oxidase and peroxidase on an automated analyzer (HITACHI 912). HbA1C level was measured with high-performance liquid chromatography standardized to the diabetes control and complications trial assay (Avantor, A9 HbA1c Analyzer) with whole blood collected in EDTA. Urine was collected from each patient (after proper education) at baseline as voided, clean-catch, midstream sample in a sterile container for routine analysis and culture and sensitivity. Samples were inoculated on Hichrome UTI agar media to determine colony-forming unit. The organisms were identified using standard culture techniques, and morphological and biochemical parameters [13]. Antimicrobial sensitivity testing was carried out on Mueller Hinton Agar (MHA) plates with commercially available discs (Kirby-Bauer disc diffusion method) and interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria [14]. Ultrasonography of the abdomen was done in all admitted patients. Blood culture and non-contrast computed tomography abdomen were done as per requirement. All the patients had their urine culture sensitivity repeated before discharge. The antibiotic treatment was given to patients depending upon symptoms and revised after receiving culture reports. Patients were followed for 6 months with regard to the number of UTIs (urine examination or culture documented) and any treatment received for the same.

Definitions

Symptomatic UTI was defined as local and systemic signs of UTI, documented pyuria, and/or accompanying microbial pathogen in urine. Acute kidney injury (AKI) was defined as increase in serum creatinine >0.3 mg/dl with 48 h or increase in serum creatinine >1.5 times baseline which is known or presumed to have occurred within prior 7 days and recurrence of UTI as repeat UTI after 2 weeks.

Statistical analysis

Data was analyzed using statistical package for Social Sciences Statistical Software version 20 (IBM SPSS statistics for Windows, version 20 Armonk, NY: IBM Corp.). Categorical variables were compared employing chi-square and Fischer's exact tests whereas continuous variables were compared by using Student's *t*-test for independent observations. To study the joint effects and interactions of various independent variables, binary logistic regression analysis was carried out to calculate multivariate *p* value. *p* value was calculated as two-tailed and a value < 0.05 was considered statistically significant.

Results

Demographic characteristics

Among two hundred patients of diabetes admitted with symptomatic UTI, women (n=162) outnumbered men (n=38). Most of these women were post-menopausal (76.5%) and had longer duration of diabetes (11.75 years in women against 7.5 years in men). Obesity and diabetes-related complications were more common in women than men (Table 1).

Clinical characteristics

All the patients presented with either symptoms of lower (dysuria, urgency) or upper UTI (flank pain, fever, nausea, and vomiting). Half of the total patients presented with cystitis (55%) and almost equal number presented with pyelonephritis (44%). UTI was complicated by emphysematous pyelonephritis (EPN) in 9.5% (n=19), AKI in 26% (n=52), and bacteremia in 23.5% (n=47). EPN was exclusively seen in women (Figure 1). Details of clinical and lab parameters in patients with EPN are summarized in Table 2.

Table 1 Baseline clinical characteristics of T2D patients with UTI

Characteristics	Female	Male	*p* value
Number of patients	162 (81%)	38 (19%)	-
Age in years	54.53±9.88	59.89±6.98	0.002
Diabetes duration in years	11.75±6.66	7.59±4.09	0.000
Retinopathy	102 (63%)	10 (26.3%)	0.000
Nephropathy	97 (59.9%)	10 (26.3%)	0.000
Symptomatic UTI prior to study	54 (33.3%)	51 (13.2%)	0.014
BMI (kg/m^2)	27.06±4.39	22.50±3.95	0.000
Obesity BMI ≥25 kg/m^2)	104 (64.2%)	17 (44.7%)	0.027

Values in mean± SD unless indicated; values in parenthesis indicate percentages

Microbiological results

Growth of pathogenic bacteria in urine was seen in 68% women (*n*=111) and 84% men (*n*=27). Duration of diabetes was longer in patients with bacteriuria than those without bacteriuria. The frequency of severe symptoms of UTI like altered sensorium and fever was more seen in patients with positive urine cultures than those with negative cultures, so were complications like EPN and AKI. Factors like chronic kidney disease (CKD), renal calculi, or cysts were commonly or exclusively seen in bacteriuric UTI (Table 3).

Table 2 Clinical and laboratory characteristics of patients with emphysematous pyelonephritis

Variable	*n* (%) patients
Females	19 (100)
Fever/chills	61 (80)
Flank pain	17 (90)
Vomiting	6 (32)
Dysuria	11 (58)
Renal angle tenderness	11 (58)
Altered sensorium	5 (26%)
Hypotension (SBP <90 mm Hg)	4 (21%)
Thrombocytopenia	6 (32)
Acute renal failure	13 (68)
Severe hypoalbuminemia (<3 g/L)	11 (58)
Class1	3 (16)
Class 2	4 (21)
Class 3a	4 (21)
Class 3b	6 (32)
Class 4	2 (10)
Medical therapy alone	9 (47.5)
Medical therapy + percutaneous catheter drainage	9 (47.5)
Nephrectomy	1 (5)

Organism isolation and sensitivity pattern

Predominantly Gram-negative organisms were isolated in urine (115 out of 138 pathogens isolated). Few Gram-positive and candida species were isolated (16 Gram-positive and seven candida species). *E. coli* was the most common pathogen isolated. Most of the Gram-negative bacilli were sensitive to amikacin, imipenem, piperacillin-tazobactam, and nitrofurantoin (95% isolates sensitive to amikacin, 92% to imipenem, 80% to piperacillin-tazobactam, and 77% to nitrofurantoin).

Hospital course and follow-up

Patient with cystitis received oral and those with pyelonephritis were managed with parenteral antibiotics. Antibiotics were reviewed after obtaining culture and sensitivity reports. Thirty-six out of 200 patients received antibiotic prophylaxis in the form of nitrofurantoin, cotrimoxazole, or levofloxacin. Patients were followed up at 6 months after discharge. Out of 200 patients, only 169 (84.5%) had complete follow-up. At the time of follow-up, patients were examined and urine examination and culture was done. Out of these 169 patients, 33 developed one episode, 20 had two episodes, 10 had three episodes, three had four episodes, and one patient developed five episodes of UTI. Thirty-one episodes were pyelonephritis while the rest were lower UTI and all episodes needed antibiotic treatment. On multivariate analysis, factors found to correlate with recurrent UTI (in women) included presence of CKD, renal calculi, and higher HbA1c, whereas in men these were lower eGFR and higher HbA1c. The presence of renal cyst or calculi did not predict the development of recurrent UTI in men.

Table 4 shows various baseline and follow-up parameters of T2D patients. HbA1c increased from 10.89 ± 2.20% to 11.18 ± 1.47% at follow-up. Renal parameters revealed reduction in serum creatinine with increase in eGFR ($p = 0.018$) at follow-up. Bacteriuria was still present in 29 patients at follow-up with *E. coli* being the most common organism. Patients with recurrent UTI (67 patients) had significantly higher HbA1c at follow-up (12.56 ± 0.82%) than at baseline (11.73 ± 2.42%; $p = 0.012$).

Discussion

The present study was mainly aimed at studying the clinical and bacteriological profile of symptomatic UTI in patients with diabetes admitted in Endocrine services, and follow-up of such patients for a period of 6 months. Out of 200 patients of diabetes with symptomatic UTI, there was a large female predominance (81%); majority (76.5%) were postmenopausal and had a longer duration of diabetes. Overall, an increased prevalence of UTI has been reported in women, more so in postmenopausal state [2, 15]. Duration of diabetes has been shown to have a significant

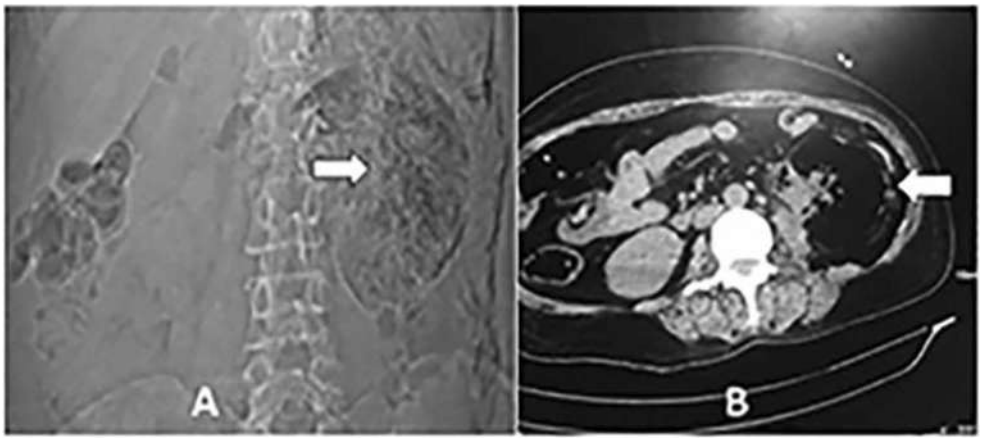

Fig. 1 Radiological changes in emphysematous pyelonephritis. **A** X-ray abdomen showing appearance of gas along left renal outline (white arrows). **B** Computed tomography of same patient showing left kidney replaced by gas (white arrows) suggestive of class -3b emphysematous pyelonephritis

correlation with prevalence of either asymptomatic bacteriuria or symptomatic UTI [16, 17]. This high prevalence may be because of development of chronic complications especially autonomic neuropathy. Autonomic dysfunction of urinary bladder is an important risk factor because of incomplete emptying of bladder and frequent need for catheterization [18]. The present study revealed that some factors like obesity, uncontrolled and longer duration of diabetes, and presence of diabetic kidney disease were significantly associated with frequency of UTI. Uncontrolled diabetes evidenced by higher HbA1c and its association with UTI is controversial. Hyperglycemia as such does not predictably increase the rate of bacterial multiplication but elevated urinary or tissue glucose impairs the neutrophil function [19, 20]. Association between nephropathy and UTI has been studied by a few, wherein micro- or macro-albuminuria has been incriminated as a risk factor for recurrent UTI [2]. In the present study, obesity and previous history of UTI significantly influenced further development of symptomatic UTI in women. The association of UTI and obesity is documented in literature [11]. Lower UTI, pyelonephritis, and bacteremia were seen both in men and women with symptomatic UTI but EPN was exclusively seen in women. This is in accordance with our previous experience that EPN is almost exclusively seen in women [21]. Acute kidney injury occurred in significantly higher percentage of women than men [11, 21].

Bacteriological profile

We documented culture positivity in 138 patients (69%). Culture positivity in our study is less than that reported in literature. One

Table 3 Clinical characteristics of patients and factors associated with bacteriuria among symptomatic UTI with T2D

Variables		With bacteriuria (*n*=138)	Without bacteriuria (*n*=62)	*p*-value	OR (95% CI)
Age in years		55.14±9.63	56.45±9.62	0.376	-
Female gender	162 (81%)	111 (80.4%)	51 (82.2%)	0.761	0.88 (0.41–1.92)
Post-menopausal	124 (76.5%)	90 (81.1%)	34 (66.7%)	0.044	2.14 (1.01–4.54)
Diabetes duration (yrs.)		11.65±6.75	9.42±5.51	0.023	
Chronic kidney disease	25 (12.5%)	23 (16.7%)	2 (3.2%)	0.009	6.0 (1.36–26.31)
Past history of SUTI	59 (29.5%)	54 (39.1%)	5 (8.1%)	0.000	7.32 (2.76–19.44)
Fever	154 (77.8%)	113 (83.1%)	41 (66.1%)	0.008	2.51 (1.26–5.02)
Altered sensorium	29 (14.5%)	27 (19.6%)	2 (3.2%)	0.002	7.29 (1.67–31.74)
Pyelonephritis	89 (44.5%)	71 (51.4%)	18 (29%)	0.03	2.59 (1.36–4.92)
EPN	19 (9.5%)	17 (12.3%)	2 (3.2%)	0.043	4.21 (1.01–18.84)
AKI	52 (26%)	47 (34.1%)	5 (8.1%)	0.000	5.88 (2.21–15.68)
Bacteremia (*n*=81)	47 (58.1%)	35 (25.4%)	12 (19.3%)	0.354	-
Pyuria	187 (93.5%)	135 (97.8%)	52 (83.9%)	0.001	8.65 (2.29–32.69)
Renal cyst	17 (8.5%)	17 (12.3%)	0	0.002	18.00 (1.06–304.38)
Renal calculi	18 (9%)	18 (13%)	0	0.003	19.19 (1.13–323.78)

SUTI symptomatic UTI, *EPN* emphysematous pyelonephritis, *AKI* acute kidney injury

Table 4 Follow-up of T2D patients with symptomatic UTI

Variables	UTI at baseline (n=169)	UTI at follow-up (n=169)	p-value
HbsA1c in %	10.89±2.20	11.18±1.47	0.110
eGFR ml/min/1.73m^2	48.86±29.61	53.80±22.22	0.018
Proteinuria	119 (70.8%)	62 (36.9%)	0.000
Bacteriuria	91 (68.4%)	29 (21.8%)	0.000
Pyuria	158 (93.5%)	32 (18.9%)	0.000
Hematuria	54 (32%)	19 (11.2%)	0.000
E. coli	95 (56.2%)	25 (14.8%)	0.248
Other organisms	21 (12.5%)	8 (4.7%)	-

study demonstrated culture positivity in 80% of symptomatic UTI in patient with diabetes [22]. The higher percentage of culture negativity in our cohort could be due to "unknowing" use of over the counter antibiotics quite common in this part of the world, although clear-cut history of antibiotic intake was an exclusion criterion for the present study. Moreover, few Indian studies also demonstrated lower rates of bacteriuria in patients with diabetes. Sharma et al. reported bacteriuria in 43% of elderly T2D patients with symptomatic UTI while Acharya et al. reported culture positivity in 34.5% of patients [23, 24]. *E. coli* was the predominant organism cultured from urine samples and was sensitive to amikacin, gentamicin, imipenem, piperacillin-tazobactam, and nitrofurantoin. A similar trend of culture growth and sensitivity pattern has been reported in other centers [25, 26]. Diabetes of longer duration, presence of previous UTI, diabetic nephropathy, renal cysts, and calculi were significantly associated with bacteriuria in our cohort of symptomatic UTI. A positive correlation between bacteriuria and duration of diabetes has been found by Smith et al. [27]. In addition, a correlation between bacteriuria and previous UTI has been documented by Yismaw et al. [28].

There were some differences seen between patients in the bacteriuria group compared with non-bacteriuric group. Fever, altered sensorium and presentation as pyelonephritis, EPN and complications like bacteremia and AKI were more often seen in bacteriuric group rather than non-bacteriuric group. Glycosuria and uncontrolled diabetes were significantly associated with bacteriuria. Yishita et al. also found an association of glycosuria and presence of bacteriuria [29]. Renal cysts, calculi, and proteinuria significantly increased the risk of bacteriuria. Proteinuria has been documented as a risk factor for bacteriuria by Geerlings et al. [30].

Follow-up

Sixty-seven patients developed UTI on follow-up; i.e., the recurrence rate was 39.6%. A higher recurrence of UTI in diabetes has been reported by other studies. In the study by Gorter et al., relapses and reinfections were respectively reported in 7.1% and 15.9% of diabetic women [10]. In a Finnish study of women aged 17 to 82 years who had *E. coli* cystitis, 44% had recurrence within 1 year [31]. On multivariate analysis, the factors found to correlate with recurrent UTI in T2D women were the presence of CKD, renal calculi, and higher HbA1c while in men these were lower eGFR and higher HbA1c. Gorter et al. showed that longer duration of diabetes and retinopathy were associated with recurrent UTI in women [10].

Renal parameters improved significantly at follow-up in most of the patients without UTI. 21.8% continued with bacteriuria at 6 months, though asymptomatic. The significance of asymptomatic bacteriuria (ASB) in this cohort of patients has not been fully understood as treatment of ASB has not been shown to decrease the prevalence of symptomatic UTI [31]. *E. coli* was the most common organism at follow-up. Among the cohort who had recurrent UTI, HbA1c was significantly higher at follow-up (12.56±0.82%) than at baseline (11.73 ± 2.42%). Renal parameters improved significantly at follow-up in non-recurrent group while these remained stable in those with recurrent UTI.

Limitations

A comparison with a parallel group is not part of the study; however, status of those who were without symptoms of UTI was confirmed on telephone. Follow-up duration could have been longer than 6 months. Study was not extended to patients of UTI attending the outpatient clinics as it is our routine to admit all the consenting patients of symptomatic UTI in the hospital and limit the outpatient treatment to asymptomatic bacteriuria [16].

Conclusion

Symptomatic UTI was much more common and severe in postmenopausal women with diabetes than in men. One in every 10 patients with UTI had emphysematous pyelonephritis. *E. coli* was the most common organism isolated, being highly sensitive to amikacin and imipenem. More than one-third of patients had a recurrence of UTI in the next 6 months. Renal parameters improved on follow-up while these remained stable in those who developed recurrent UTI during the same time.

Author contribution BAL and BAF conceived the study, followed up the patients, analyzed the data, wrote and the manuscript, MHB followed up the patients, assisted in writing and editing the manuscript, and contributed in discussion. All the authors read and approved the final manuscript.
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Data availability The dataset generated and analyzed during the study are available from the corresponding author on request.

Declarations

Ethics approval The study was approved by institutional ethics committee (IEC).

A written informed consent was obtained from all the recruited individuals and the institutional ethical committee approved the study.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Innovative mobile-health led participatory approach to comprehensive screening and treatment of diabetes (IMPACT diabetes): rationale, design, and baseline characteristics

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Abstract

Background India has 66 million people with diabetes, of which a large proportion do not receive adequate care. The primary health centres can serve as platforms for early detection of diabetes and continuum of care.

Objectives This project evaluates a community-level technology-enabled system-level intervention based around the community health workers and primary-care physicians. We hypothesize that incorporation of a mobile clinical decision support system, with other process-level changes will improve identification and management of individuals with diabetes in primary care settings.

Methods A cluster-randomized trial in sixteen villages/peri-urban areas in Andhra Pradesh and Haryana will test the feasibility and preliminary effectiveness of this intervention. The effectiveness of the extended care intervention will be evaluated by the difference in HbA1c (glycosylated hemoglobin) measured at baseline and end-line between the two study arms. Qualitative interviews of physicians, ASHA, and community members will ascertain the intervention acceptability and feasibility.

Results A total of 1785 adults (females: 53.2%; median age: 50 years) were screened. ASHAs achieved 100% completeness of data for anthropometric, blood-pressure, and blood-glucose measures. At baseline, 63% of the participants were overweight/obese, 27.8% had elevated blood pressure, 20.3% were at high-risk for cardiovascular disease (CVD), and 21.3% had elevated blood glucose. Half of the individuals with diabetes were newly diagnosed.

Conclusion Technology enabled transfer of simple clinical procedures from physicians to nonphysician health workers can support the provision of healthcare in under-served communities. Community health workers can successfully screen and refer patients with diabetes and/or CVD to physicians in primary healthcare system.

Keywords Diabetes · mHealth · ASHA · Screening · Blood glucose · HbA1c · Frontline health workers · Clinical Decision Support System

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Background

India currently has 66 million people with diabetes, and this number is projected to rise to 101 million by 2030 [1]. In 2016, diabetes accounted for 10.4 million disability-adjusted life years (DALYs) in India, an increase of 175% over 1990. Diabetes also contributes to DALYs from other conditions. For example, diabetes accounted for over 50% of the global increase in chronic kidney disease DALYs during this period [2]. The largest increase in diabetes DALYs was noted in rural communities in India, where 65% of the population currently resides, [3] posing challenges for India's fragile health system [4].

A shortage of primary care workforce, lack of an efficient community-based screening program, and provision of guideline-based clinical care undermine the efforts to manage diabetes in India. Health and wellness centres (HWCs) are central to the Indian National Health Policy's provision of comprehensive primary health care (PHC) [5]. The government plans to establish 150,000 HWCs by 2022. Innovative delivery methods, such as task-shifting and use of technology, along with improved access to medicines and diagnostics, have the potential to increase access to quality guideline-based healthcare. Task-shifting, where front-line, non-physician health workers (such as the accredited social health activists [ASHA], selected from amongst the local female residents of the village) are delegated some of the tasks traditionally performed by physicians, has been shown to improve health outcomes and processes of care [6]. Deployed primarily for maternal and child health services, they are being increasingly used to identify and manage other health conditions, including non-communicable diseases (NCDs) [7]. The potential of digital technology to improve the performance of the health workforce by providing them prompt access to job-aids and clinical decision support system (CDSS) has been increasingly recognized [8]. Various systematic reviews have outlined the role of CDSS to deliver appropriate healthcare [9, 10], but the evidence for their effectiveness and feasibility in primary healthcare is still fragmented [11].

Methods

Objectives

The IMPACT diabetes is a proof of concept randomised trial that aims to develop and evaluate a bespoke diabetes management program that empowers ASHA and PHC doctors through a mobile platform–based CDSS embedded in the public healthcare system to improve the identification and management of diabetes. The primary objective of the study is to evaluate the effectiveness of the extended care intervention by observing the difference in HbA1c (glycosylated hemoglobin) measured at baseline and end-line. The main secondary objective is to ascertain the acceptability and feasibility of the proposed intervention by conducting qualitative interviews of physicians, ASHAs, and community members.

Overall design and methods

Development of the CDSS

The George Institute for Global Health has developed Systematic Medical Appraisal Referral, and Treatment (SMARThealth), a mobile-based cardiovascular disease (CVD) referral and management platform for use in the primary healthcare system. The process of development and field-testing of the SMARThealth CVD has been published elsewhere [12]. Briefly, the package consists of a 7-inch tablet running android operating system with the CDSS application, training and resource support for ASHA and primary care physicians, shared electronic record functionality using open medical record system (open MRS), a prompt system for referral and follow-up, ensuring medication supply, and remuneration for the ASHAs. Data uploads occur whenever a network connection is available. ASHAs make electronic referrals to the PHC physicians and get alerts after the physician has confirmed the diagnosis and prepared a management plan.

The platform was expanded to integrate assessment and management protocols for diabetes and its complications. The process of CDSS development was as follows: we developed a plain language algorithm for screening and management of diabetes based on the review of the current Indian [13] and international guidelines [14, 15], followed by a three-step process for the validation of the algorithm. Firstly, a group of expert physicians reviewed the plain language algorithm to assess the appropriateness of pharmacological and lifestyle recommendations. The algorithm was then converted into a statistical and programming code. In the second step, a researcher not involved with the algorithm development was given the plain language algorithm summary along with mock input data from 200 patients. Programming modifications in the statistical code were made, where necessary. Finally, the plain language rules were built as a java-based application. De-identified data from a large cross-sectional study (approximately 10,000 patients) was run using both the statistical and the programming codes. Correlation for each of the calculated variables between those generated from the programming code and the statistical code was assessed. Changes were made in the application until 100% consistency was obtained between both the outputs. The final programme code was integrated with the existing SMARThealth platform. The English language strings were translated into local languages (Telugu and Hindi) for field-testing the integrated platform.

Study design and sites

The study is a population-based, pragmatic cluster–randomized trial conducted in the public healthcare systems in two locations: rural areas of Guntur district of Andhra Pradesh and peri-urban centres in Rohtak district in Haryana. A total of 8 PHC facilities were selected in the two study areas (Fig. 1) in consultation with respective district health authorities. Within each PHC, two villages (in case of Guntur) or peri-urban areas (in case of Rohtak) were randomly selected from the list of 35 villages/areas.

Eligibility and recruitment

Within each village/area, one ASHA was assigned to screen approximately 100 community members over the age of 30 years. Participants were excluded if they had any physical illness that prevented follow-up, any intellectual disability that prevents them from following instructions or responding to the questionnaire, or if the participant is unlikely to stay in the community for the duration of the study. Pregnant women were also excluded. ASHAs screened the participants using capillary blood glucose testing (Fig. 2) in their households during their routine health promotion work. Glycosylated hemoglobin (HbA1c) test was performed on participants with random blood glucose (RBG) ≥ 200 mg/dL or fasting blood glucose (FBG) >126 mg/dL), as per the Research Society for the Study of Diabetes in India (RSSDI) clinical practice guidelines [13]. The HbA1c testing was performed by an accredited laboratory in compliance with National Glycohemoglobin Standardization Programme.

Intervention

Study intervention, information dissemination strategies, and recruitment methods were developed in consultation with the local community members, ASHAs, and healthcare professionals. Subjects with elevated blood glucose levels were referred to the participating PHC physicians. Using the SMARThealth CDSS, the physicians prescribe guideline-based medications from the essential medicine list and provide evidence-based recommendations on blood glucose and blood pressure (BP) monitoring, and lifestyle changes (Fig. 3). After physician consultation, ASHAs receive system–generated alerts on their devices about the follow-up schedules. ASHAs repeat the lifestyle recommendation and emphasize the need for treatment adherence and regular follow-up during household follow-up visits. Table 1 highlights the difference between the care facilities provided to the participants in the control and intervention areas. Participants with normal HbA1c received lifestyle modification recommendations from ASHAs and were advised a follow-up blood glucose testing after 12 months. Those found to have normal capillary blood glucose values were advised to get follow-up testing after 3 years.

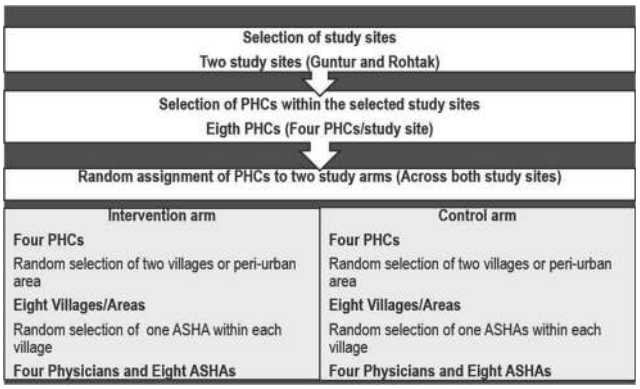

Fig. 1 Sampling technique and randomization scheme for the study. PHC — primary health centres; ASHAs — accredited social health activists

Training

A training program was developed and provided to ASHAs and PHC physicians on the use of SMARThealth platform. The training manual included modules on screening and management for diabetes, its complications and CVD risk; the use of the mobile application, screening methodology, interpretation of the decision support output, context-specific management advice, and blood pressure and capillary blood sugar measurement. The training material was developed in Hindi and Telugu for use in Rohtak and Guntur respectively. The duration of the first spell of training was 5 days, followed by a minimum of 3 days of field practice. Booster training was provided after 2 weeks. PHC physician training involved one-on-one guidance in the use of the electronic data collected by the ASHAs, and interpretation of the CDSS output for management decisions.

Measurements and confirmation of diagnosis

The ASHA collected demographic and clinical data and measured height, weight, BP, and capillary blood glucose for each participant. We used A&D UA-767 Plus Bluetooth-enabled digital BP monitors (A&D Limited, Tokyo, Japan). Three readings were taken 2 to 3 min apart, and the average of the second and the third reading was taken as the final BP for each participant [16]. Abbott FreeStyle Optium Neo (Abbott Diabetes Care Inc, CA, USA) monitors were used for the measurement of capillary blood glucose.

Hypertension is defined as systolic blood pressure (SBP) of ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg (20) and/or self-reported use of antihypertensive drugs. As per the RSSDI clinical practice guidelines, diabetes is defined as capillary RBG levels of ≥200 mg/dL or self-reported use of glucose-lowering drugs [13]. For those with RBG of 140–199

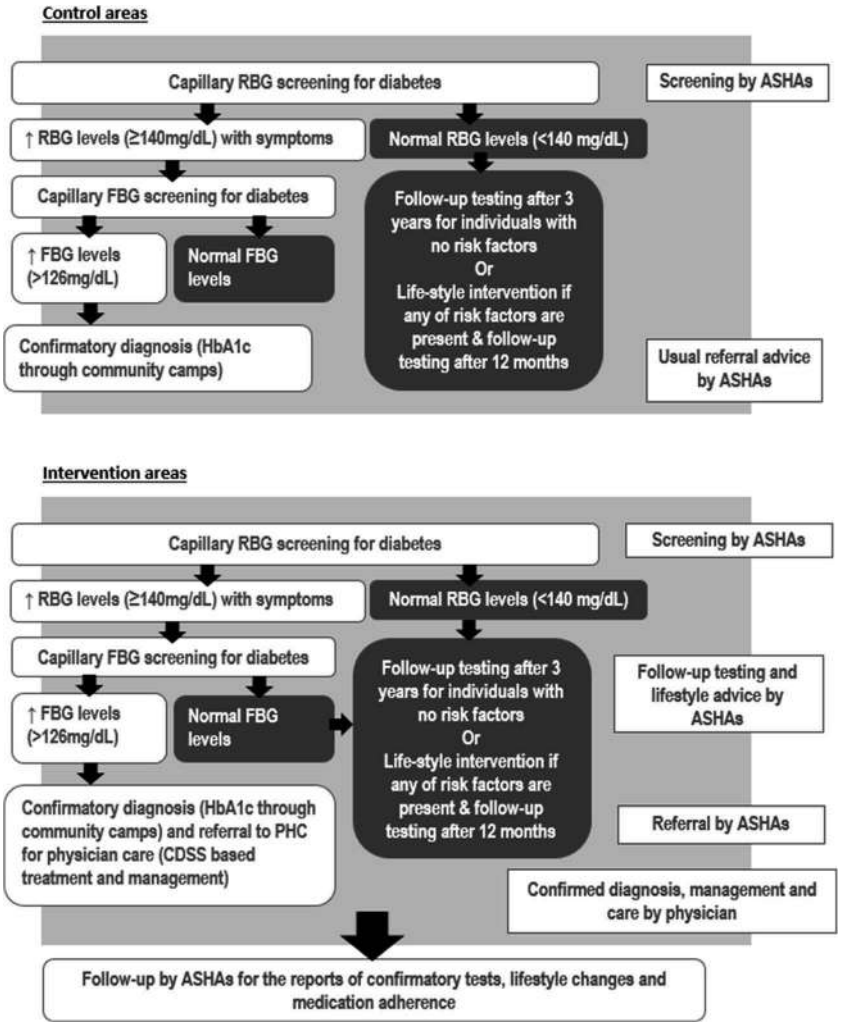

Fig. 2 Illustration of the intervention design. PHC — primary health centres; ASHAs — accredited social health activists; RBG — random blood glucose; FBG — fasting blood glucose; HbA1c — glycosylated haemoglobin; CDSS — clinical decision support system

mg/dL, a capillary FBG test was done at home within 1 week of their RBG test, and a value >126 mg/dL was required for the diagnosis of diabetes. Participants with raised blood glucose levels underwent HbA1c testing. World Health Organization/International Society of Hypertension (WHO/ISH) low information prediction chart are used to measure the 10-year risk of a cardiovascular event (myocardial infarction or stroke) [17].

PHC visit and ASHA follow-up

In the intervention arm, a laboratory technician measured the BP and RBG of the participants at the PHC. The physicians review lifestyle advice given by ASHAs, and provide pharmacological advice with the aid of the SMARThealth CDSS. The ASHAs can track the visit and do follow-up visits to record BP, blood glucose, and adherence to prescribed medications using the Morisky medication adherence scale [18]. If any medical care is received outside the PHC (due to prevalent practice), the ASHA records the details of the type of health facility visited and reasons for not visiting PHC.

End of the study

HbA1C test will be repeated after 9 months. Focus group discussions (FGD) and semi-structured interviews of physicians, ASHAs, and community members will be conducted to ascertain the acceptability and implementation feasibility of the intervention. Semi-structured interviews and FGD guidelines will be developed based on the review of the literature and research questions. Interviews will be conducted by researchers experienced in these field settings.

Outcomes measures and analyses

Quantitative measures The primary outcome measure will be the difference in the proportion of participants with diabetes showing a 0.5% reduction in HBA1c [19]. An a priori power calculation indicated that 10 participants with diabetes are needed per cluster to detect a 20% additional reduction in the intervention group as compared with the control group. Using two-sided tests at a significance level of 5%, and intraclass correlation coefficient (ICC) of 0.03 (based on our previous work [20],

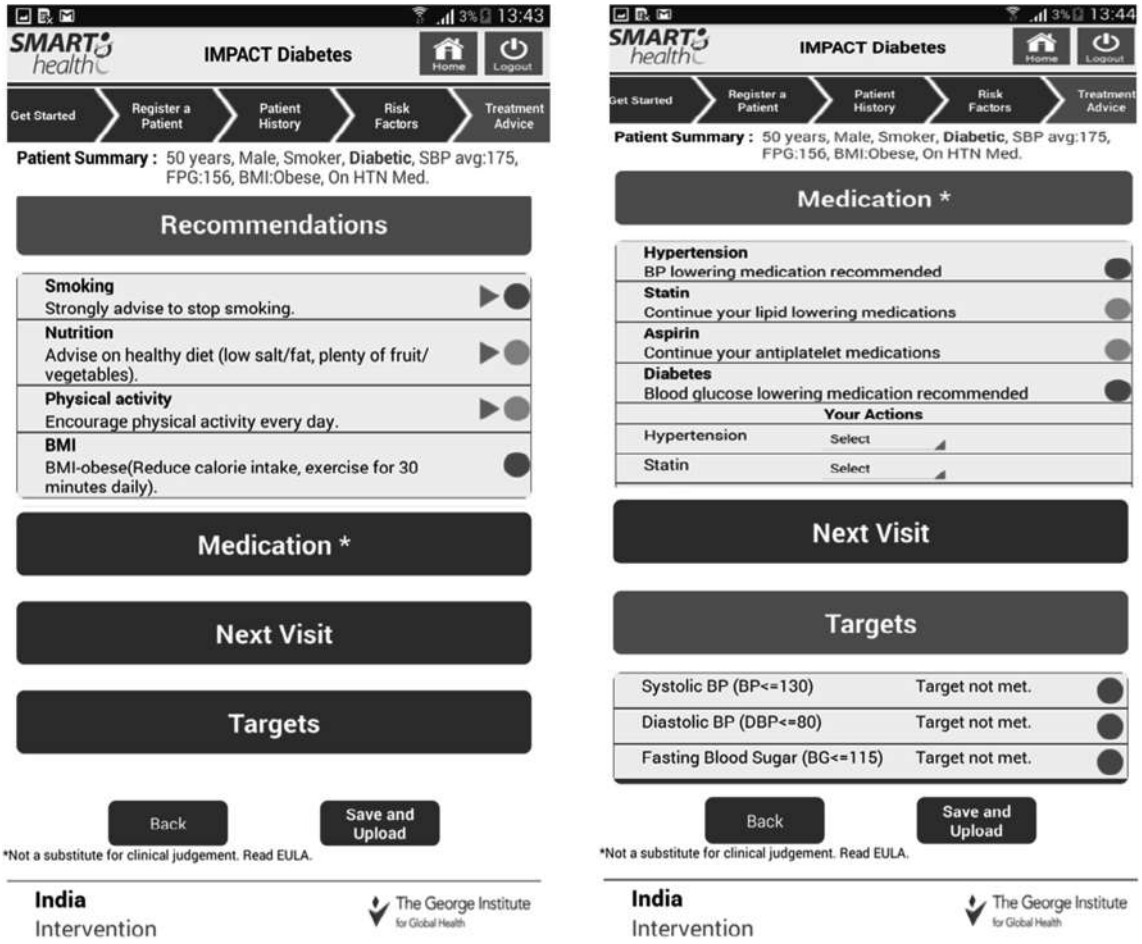

Fig. 3 Nutritional, pharmacological, and behavioural risk factor management recommendations provided by PHC physicians

we can achieve a statistical power of 80%. Secondary outcome measures include proportions of individuals visiting a physician and adherence to blood glucose–lowering medications.

Qualitative measures The acceptability and feasibility of the intervention will be ascertained through the understanding of (i) ASHAs' and physicians' experience with the intervention, (ii) impact of CDSS on staff's usual work routines and knowledge, and (iii) patient satisfaction with the treatment and management recommendations.

Analysis

Inferential statistical analysis will be performed on an intention-to-treat basis. Student's *t* test and one-way analysis of variance (ANOVA) will be applied to compare continuous variables, and the chi-squared test will be used to compare categorical variables. Due to the clustered study design, the primary outcome will be assessed using a generalized linear mixed regression model. *p* values of less than 0.05 will be considered statistically significant. Within-trial economic evaluation will be conducted to evaluate the incremental costs per quality-adjusted life-years gained and cost per 0.5% reduction in HbA1c. The intervention cost will be based on salaries, training, equipment, and other costs incurred with the implementation of the intervention.

All interviews and FGDs will be digitally recorded, professionally transcribed, and translated to English. We will verify 10% of the randomly selected transcriptions against the recordings for quality control. Thematic content analysis of the transcriptions and field notes will be performed using NVivo software (version 11). Two members from the research team will code transcripts based on the following deductive (a priori) codes: (i) facilitators and barriers for quality NCDs and diabetes management in resource-poor settings, (ii) satisfaction with the training, (iii) perceived usefulness and difficulties of the CDSS, (iv) perception on the behaviour change intervention package, (v) impact on work routines, and (vi) ASHAs', doctors', and participants' satisfaction. Significant inductive (emerging) codes will also be identified. Coded items will be grouped into distinct themes, drawing on the methods outlined by Patton [21]. The inter-coder reliability will be checked, and a Kappa-statistic will be calculated. A third qualitative researcher will adjudicate discrepancies.

Table 1 Summary of the differences between the care facilities

Comparison of the facilities	Control areas	Intervention areas
Screening by ASHA within the community (using blood glucose strip method and BP measurement)	✓	✓
General information on the causes and management of diabetes	✓	✓
Information on diabetes-related complications and uncontrolled blood glucose		✓
Referring the screened positives for confirmative testing	✓	✓
Confirmative testing reminders	✓	✓
Referral of suspected cases to PHC for treatment advise	✓	✓
Electronic medical information exchange between ASHA's and the PHC physician		✓
Setting up a diabetes management plan (including smoking cessation, weight loss, improved diet, aerobic exercise, alcohol and sodium restriction, treatment by medication, and adherence to medications)		✓
Engagement of family members in diabetes management		✓
Follow-up visits by ASHAs and telephone reminders for diabetes management		✓
ASHAs to identify problems related to diabetes management and screen for related complications		✓
Reporting the identified problems and complications (including hypoglycaemia, ocular complications, kidney disease, foot care, and neuropathy) to the PHC physician		✓
Periodic monitoring of blood glucose levels as per the Indian guidelines		✓
Increased frequency of contact with patients showing poor management		✓

Ethical considerations

Ethical approvals were obtained from the Institutional Ethics Committees of Centre for Chronic Disease Control, New Delhi (FWA00012746), and PGIMS, Rohtak, Haryana (IEC/18/524). All the study participants provided written informed consent.

Results

The recruitment was carried out between January and August 2019 in Guntur and between August 2019 and January 2020 in Rohtak. Table 2 present the baseline characteristics of the participants. A total of 1785 participants, 53.2% females and median, (inter-quartile range, (IQR)) age of 50 (40–61) years

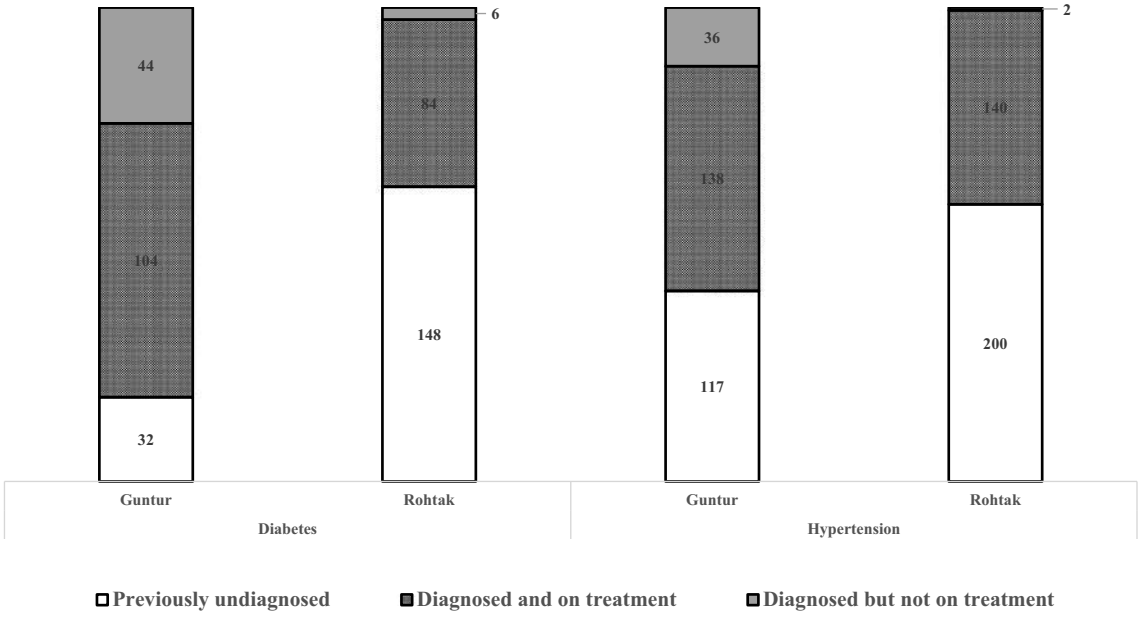

Fig. 4 Self-reported diagnosis and treatment history of the participants with hypertension and diabetes

Table 2 Participant baseline demographic characteristics, medical and family history, and metabolic characteristics

Characteristics	Female (*n*=949)	Male (*n*=836)	Total (*n*=1785)
Age, years	51 (40–60)	50 (39–62)	50 (40–61)
Weight, kg	60 (52.0–69.0)	64 (56.0–73.3)	62 (54.0–71.0)
BMI, kg/m^2	25.4 (22.1–28.9)	23.9 (21.2–27.0)	24.6 (21.5–28.0)
Underweight (<18.0)	70 (8.0%)	92 (10.1%)	162 (9.1%)
Normal (18.0-22.9)	238 (27.2%)	263 (28.9%)	501 (28.1%)
Overweight (23.0-24.9)	138 (15.8%)	151 (16.6%)	289 (16.2%)
Obese (>25)	503 (57.4%)	330 (36.3%)	833 (46.7%)
Tobacco use			
Current smoker	24 (2.7%)	295 (32.5%)	319 (17.9%)
Past smoker[a]	3 (0.3%)	16 (1.8%)	19 (1.1%)
Current chewing	5 (0.6%)	48 (5.3%)	53 (3.0%)
Past chewing[b]	0 (0.0%)	4 (0.4%)	4 (0.2%)
Medical history			
Diabetes	147 (16.8%)	107 (11.8%)	254 (14.2%)
Angina/heart attack	42 (4.8%)	46 (5.1%)	88 (4.9%)
Stroke	20 (2.3%)	23 (2.5%)	43 (2.4%)
Hypertension	224 (25.6%)	121 (13.3%)	345 (19.3%)
Peripheral vascular disease	4 (0.5%)	5 (0.6%)	9 (0.5%)
Family history[c]			
Diabetes	192 (21.9%)	157 (17.3%)	349 (19.6%)
Angina/heart attack	89 (10.2%)	90 (9.9%)	179 (10.0%)
Stroke	73 (8.3%)	58 (6.4%)	131 (7.3%)
Medication history			
Anti-hypertensive	177 (20.2%)	101 (11.1%)	278 (15.6%)
Antiplatelet	16 (1.8%)	13 (1.4%)	29 (1.6%)
Lipid lowering	8 (0.9%)	7 (0.8%)	15 (0.8%)
Blood glucose-lowering	115 (13.1%)	73 (8.0%)	188 (10.5%)
Hypertension[d]	346 (36.5%)	287 (34.3%)	633 (35.5%)
Controlled BP[e], on treatment	83 (8.7%)	53 (6.3%)	136 (7.6%)
Grade 1 hypertension[f]	189 (21.6%)	150 (16.5%)	339 (19.0%)
Grade 2 hypertension[g]	47 (5.4%)	55 (6.1%)	102 (5.7%)
Grade 3 hypertension[h]	27 (3.1%)	29 (3.2%)	56 (3.1%)
Isolated systolic hypertension [i]	80 (9.1%)	56 (6.2%)	136 (7.6%)
SBP, mmHg	116 (106.0–131.0)	120 (110.0–132.0)	118 (108.0–132.0)
DBP, mmHg	79 (72–87)	82 (74–88)	81 (73–87)
10-year risk of fatal and non-fatal CVD[j]	186 (21.2%)	176 (19.4%)	362 (20.3%)
Diabetes [k]	232 (26.5%)	186 (20.5%)	418 (23.4%)
Controlled, on therapy	21 (2.2%)	16 (1.9%)	37 (2.1%)
Blood glucose, mg/dL	103 (87.0–123.0)	101 (87.0–124.0)	102 (87.0–124.0)

[a] Has not smoked tobacco in the past 12 months; [b] has not chewed tobacco in the past 12 months; [c] first-degree relatives (father, mother, and siblings) diagnosed with the disease; [d] currently on antihypertensive drugs or SBP: ≥140 mmHg and/or DBP: ≥90 mmHg; [e] Optimal/normal blood SBP: <120–139 mmHg and/or DBP: <80–89 mmHg , [f] grade 1 hypertension SBP: 140–159 mmHg and/or DBP: <90–99 mmHg, [g] grade 2 hypertension SBP: 160–179 mmHg and/or DBP: 100–109 mmHg; [h] grade 3 hypertension SBP: ≥180 mmHg and/or DBP: ≥110 mmHg; [i] isolated systolic hypertension SBP: ≥140 and DBP: <90; [e–i] are based on the ESC/ESH guidelines (20); [j] based on WHO/ISH cardiovascular risk prediction charts; [k] currently on blood glucose-lowering drugs or capillary RBG ≥ 200 mg/dL or capillary FBG >126mg/ dL

were screened. We achieved 100% completeness of data for all anthropometric, BP, and blood glucose measures (Table 2). ASHA screenings revealed that 27.8% of the screened participants had an elevated BP, 21.3% had elevated blood glucose, and 20.3% had a high 10-year CVD risk (Table 2).

Figure 4 presents the self-reported diagnosis and treatment history of the participants with hypertension and diabetes. Half of the participants with hypertension and 43% of the participants with diabetes were newly diagnosed.

Discussion

The encouraging completion rates of anthropometric, BP, and blood glucose measures in this multicomponent health-system intervention embedded in routine primary care practice settings reiterates that with training and retraining, the ASHA are able to identify individuals with hypertension and diabetes, and can contribute to improving efficiency of service delivery [22]. While the ASHAs are used to completing a paper-based assessment checklist and motivate the community members to visit the community-based screening camps, the current intervention goes beyond and allows them to accurately identify those in need for referral using an automated electronic decision support system.

The effectiveness of the SMARThealth platform in linking community-based assessments to doctor level care has been tested in the areas of CVD and mental health [23, 24]. The addition of BP and blood glucose testing allowed expansion of the capability of the platform but also challenges the argument that ASHA cannot acquire such skills. The role of technological innovations is important in resource-poor settings of India, where the health system has been criticized for its unacceptably low quality and poor effectiveness [25]. Recent systematic reviews has shown that integration of mobile technology within the health system can overcome challenges related to service accessibility and treatment quality in primary care settings in India [10, 26, 27]. In a recent cluster randomised trial, Prabhakaran et al. found that electronic decision support for healthcare providers was not better than 'enhanced usual care' in management of blood pressure or diabetes in community [28]. Despite the null result, the trial showed that implementation of an mHealth intervention tool was feasible.

The baseline data provides us information about anthropometric and metabolic characteristics of the study subjects. Of note is the high proportion of undiagnosed cases of hypertension and diabetes in the community. Several national and state-level community-based studies have reported similar findings. A cross-sectional study of 5127 individuals in the state of Punjab revealed that 70% of the people with hypertension were undiagnosed or untreated [29]. Similarly, the Indian Council of Medical Research India Diabetes Study (n=57,117 in 14 states) found that 47.3% of participants with diabetes were previously undiagnosed [30]. These studies were done 6 to 10 years ago, and the proportion of untreated cases has remained unchanged despite the increasing awareness of NCDs, reinforcing the need to bring in a new approach.

A strength of the study is its pragmatic design that allows the utilization of existing care pathways in the Indian primary care systems. The existing workforce will implement this multicomponent intervention in the context of their current roles and responsibilities and during their routine health promotion work, obviating the need for additional household visits. The combination of quantitative and qualitative findings would help identify key components of the health system that might need strengthening for prevention and management of NCDs. Implementation in two geographies and health systems will provide information around the generalisability of the findings.

The study also has some limitations. The main purpose of this feasibility study is to obtain preliminary estimates (such as the variance of treatment effect) that can be used for planning a larger trial. Due to the limited sample size, our study may be underpowered to detect a true effect of the intervention. Secondly, because of the non-random selection of the participants, we would not be able to estimate the true prevalence of diabetes. However, based on the study objectives, we have chosen outcomes that are meaningful for routine practice.

In conclusion, the IMPACT diabetes study will provide evidence whether transfer of simple clinical procedures from physicians to non-physician health workers and judicious use of technology can be effectively deployed for managing diabetes and its complications in underserved communities. Findings of this study would feed into a larger trial that would provide information on process measures and the cost-effectiveness of this multicomponent intervention.

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Ethics approval and consent to participate Ethical approvals were obtained from the Institutional Ethics Committees of Centre for Chronic Disease Control, New Delhi (FWA00012746), and PGIMS, Rohtak, Haryana (IEC/18/524). All the study participants provided written informed consent.

Competing interests The authors declare no competing interests.

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ORIGINAL ARTICLE

Current insulinization trends in India

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Abstract

Background Hyperglycemia-associated micro- and macro-vascular complications remain the leading cause of premature morbidity and mortality among the diabetic population worldwide. Poor glycemic control due to clinical inertia towards insulin treatment is a major cause behind the development of diabetic complications. In this paper, we analyze different strategies of insulin treatment initialization and titration practiced in India.

Methods The response of 367 healthcare professionals (HCPs) across the country was recorded based on a survey on demographics, treatment regimens, and patient behavior. For analysis, the responses from HCPs were segregated into six regions, north, south, east, west, and central, covering the entire country.

Results The survey revealed that 59.1% HCPs preferred using three oral anti-diabetic drugs (OADs) before starting insulin therapy while 12.5% initiated insulin as the last option after trying all available OADs. Besides, 61% HCPs across India considered initiating insulin in type 2 diabetes mellitus (T2DM) patients when the patients (i) failed to achieve glycemic targets with current OADs, or (ii) could not tolerate OADs, or (iii) required a more flexible therapy. In T2DM patients, 52.9% HCPs chose basal only insulin during initiation. In comparison, 63.8% HCPs used basal bolus while initiating insulin in type 1 DM (T1DM) patients. Pan-India, 53.4% HCPs preferred analogue premix while 46.6% HCPs opted for human premix. Next, 98.9% HCPs counselled patients about the risk of hypoglycemia upon initiation of insulin.

Conclusion This survey outlines an urgent need of reducing the clinical inertia against insulin initialization in Indian settings.

Keywords Insulinization · Diabetes management · Insulin regimen · Clinical inertia · Hyperglycemia · Oral anti-diabetic drugs

Introduction

Oral hypoglycemic agents remain the first line of treatment among the patients suffering from T2DM. Due to the failure of oral hypoglycemic agents in maintaining satisfactory blood glucose levels, insulin therapy remains the preferred line of treatment in a substantial number of diabetic patients. It is estimated that 4–10% of patients with T2DM rely on insulin in combination with oral hypoglycemic agents [1, 2]. Most diabetic patients (T1 or T2) require insulin therapy at least at one or other point in their life to achieve satisfactory control over hyperglycemia [3].

Initiation and implementation of insulin therapy among diabetic patients remain a challenging task for healthcare providers [4]. For instance, trypanophobia (fear of needles) is a major psychological barrier, while the risk of developing hypoglycemia among patients defying their physician's prescribed dose of insulin per day is another challenge due to

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inconvenient treatment schedules. All these reasons result in clinical inertia towards insulin treatment and subsequently lead to rising numbers struggling with diabetes-related complications such as retinopathy, neuropathy, and nephropathy [5–9].

While there is global consensus on the early initiation of insulin to maintain tight glycemic control and delay the onset of complications [10], it is often seen that substantial proportion of the Indian population with diabetes fails to achieve glycemic targets [11]. A survey by the diabetes-attitudes-wishes-needs (DAWN) program revealed that Indian physicians take a significantly longer time to start insulin treatment post-diagnosis than physicians from other countries. Physicians prefer to delay insulin initiation to achieve higher insulin efficacy as well as to gain patient acceptance and compliance [12].

Consequently, physicians tend to overuse the traditional therapies or oral anti-diabetic drugs (OADs) for diabetes care, either to retain patients or due to a lack of proper information on introducing insulin [13]. In most cases, insulin therapy is taken into consideration when HbA1c levels increase to >9%, and/or in the cases of lipotoxicity and glucotoxicity [14]. In addition, being a vast and diverse country in terms of food and socio-cultural habits, the geographical regions of India present heterogeneity in the distribution of diabetes burden, which also affects the insulin initiation strategies for long-term management of DM patients.

The current study aims to analyze insulin initiation practices prevailing across distinct parts of India with a focus on care, clinical, and behavioral variables.

Materials and methods

A survey was designed to collect the opinion of healthcare professionals from across the country practicing and managing DM. This survey comprised 23 questions encompassing the field of practice of HCPs, area of practice (rural or urban), their reason behind prescribing insulin, and their choice of insulin for initiation and titration. The complete list of questions is provided as a Supplementary Information file (SI 1). The survey was circulated among the HCPs from the Research Society for the Study of Diabetes in India (RSSDI) through an email database and among the HCPs who were non-members but part of local associations and actively involved in managing DM. A total of 367 responses were received. The responses received from the survey were analyzed and studied.

Responses were segregated based on geographical regions—north, south, east, west, and central India to study and distinguish insulin initiation patterns across the country. Analysis of collected data was performed at both the country level and the regional level. The analysis also included responses from retrospective data collection from regular clinical practice from 6 different diabetes care centers.

All variables studied were classified into three categories: (i) care characteristics, (ii) clinical characteristics, and (iii) behavioral characteristics. Care characteristics included information on the field of practice of HCPs, their experience and area of practice (rural or urban), and counselling practices on management techniques and expected risks. Clinical characteristics comprised of the reasons behind prescribing insulin, number of OADs before initiating insulin, most common type of insulin initiated (for both T1DM and T2DM), dosage and monitoring frequency, up-titration of basal insulin, and preference of premix (analogue or human). Behavioral characteristics enlisted factors that HCPs considered before initiating insulin in DM patients including patient incompliance.

Categorical variables were presented as numbers (percentages). Data were expressed as values with a 95% uncertainty interval (UI). All statistical analyses were conducted using Prism software (version 9; GraphPad).

Results

Care characteristics

Table 1 lists region-wise and pan-India responses to care characteristics included in the survey. Among the total of 367 responses received from HCPs across the country, 47.4% were from diabetologists, 33.2% were from physicians, 16.1% were from general physicians, and 3.3% were from endocrinologists. Region-wise, the percentage of diabetologists was highest in all regions except in the central region where the number of physicians was 5.2% more than the number of diabetologists. Endocrinologists constituted the lowest proportion among all HCPs who responded to this survey. 71.4% of practitioners who were treating DM patients country-wide had a clinical experience of more than 10 years. A similar trend resonated with all regions except the central region where 51.3% of practitioners had clinical experience between 5 and 10 years, and 35.9% had more than 10 years of working experience. We also noted that 80.9% of all the HCPs surveyed across India were practicing in urban areas. Further, it should be noted that a significant percentage (98.9%) of the responding physicians indulged in extensive counselling and personal care of their respective patients for a better lifestyle to counter the challenges of DM.

Clinical characteristics

Table 2 represents region-wise and pan-India responses to clinical characteristics included in the survey. According to the analysis, 61% HCPs across India responded that they considered initiating insulin in T2DM patients when the patients

Table 1 Care characteristics. The table provides a segmented analysis of the consulting physician's characteristics actively involved in managing diabetes. The segregated columns in the table have been done based on practicing regions of the healthcare professionals (HCPs) for understanding the demographic trends

Variable	Pan-India (*n*=367)	North (*n*=57)	South (*n*=151)	East (*n*=54)	West (*n*=66)	Central (*n*=39)
Physician specialty, *n* (%)						
Diabetologist	174 (47.4)	28 (49.1)	67 (44.4)	28 (51.85)	35 (53)	16 (41)
Endocrinologist	12 (3.3)	2 (3.5)	3 (2)	2 (3.7)	3 (4.5)	2 (5.1)
General physician	59 (16.1)	12 (21.1)	29 (19.2)	5 (9.26)	10 (15.2)	3 (7.7)
Physician	122 (33.2)	15 (26.3)	52 (34.4)	19 (35.2)	18 (27.3)	18 (46.2)
Number of years in practice of diabetes, *n* (%)						
1–2 years	9 (2.45)	2 (3.5)	4 (2.6)	0 (0)	2 (3)	1 (2.6)
2–5 years	37 (10.08)	4 (7)	13 (8.6)	5 (9.3)	11 (16.7)	4 (10.3)
5–10 years	59 (16.07)	6 (10.6)	21 (13.9)	6 (11.1)	6 (9.1)	20 (51.3)
10 years and above	262 (71.4)	45 (78.9)	113 (74.5)	43 (79.6)	47 (71.2)	14 (35.8)
Area of practice, *n* (%)						
Urban	297 (80.9)	53 (93)	114 (75.5)	41 (75.9)	53 (80.3)	36 (92.3)
Rural	70 (19.1)	4 (7)	37 (24.5)	13 (24.1)	13 (19.7)	3 (7.7)
Counselling patient about risk of hypoglycemia on insulin initiation, *n* (%)						
Yes	363 (98.9)	57 (100)	149 (98.7)	54 (100)	64 (97)	39 (100)
No	4 (1.1)	0 (0)	2 (1.3)	0 (0)	2 (3)	0 (0)
Counselling patient about a diabetic meal plan that matches calories from foods (carbohydrates, proteins, and fats or oils) to individual body activity and insulin levels, *n* (%)						
Yes	356 (97)	55 (96.5)	147 (97.4)	53 (98.1)	62 (93.9)	39 (100)
No	11 (3)	2 (3.5)	4 (2.6)	1 (1.9)	4 (6.1)	0 (0)
Teaching insulin initiation techniques to the patients, *n* (%)						
Insulin advisor/diabetes educator	112 (30.5)	20 (35.1)	40 (26.5)	8 (14.8)	17 (25.8)	27 (69.2)
Me myself	218 (59.4)	34 (59.6)	91 (60.2)	43 (79.6)	39 (59.1)	11 (28.2)
My staff (non-trained)	19 (5.2)	2 (3.5)	10 (6.6)	0 (0)	7 (10.6)	0 (0)
Patient is asked to refer to YouTube	1 (0.3)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)
Pharma colleague	17 (4.6)	1 (1.8)	9 (6)	3 (5.6)	3 (4.5)	1 (2.6)

(i) failed to achieve glycemic targets with current OADs, or (ii) could not tolerate current OADs, or (iii) were in requirement of a more flexible therapy (Fig. 1). In addition, 59.1% of the HCPs surveyed country-wide resorted to using three OADs before initiating insulin therapy while 12.5% preferred to start insulin as the last option after trying all available OADs. In T2DM patients, 52.9% HCPs chose to use basal only as the preferred type of insulin during initiation (Fig. 2b). On the other hand, basal bolus was the choice of 63.8% HCPs while initiating insulin in T1DM patients, as shown in Fig. 2a. The average country-wide preferences in choosing between analogue and human premix insulin were mixed. Pan-India, 53.4% HCPs preferred analogue premix while 46.6% HCPs opted for human premix. In the case of patients with gestational diabetes mellitus (GDM), there are other additional factors that need to be taken into consideration while deciding on initiating insulin therapy. Some of the important considerations include whether (i) the patient has already been on glibencalmide, (ii) the patient has already been on metformin, (iii) the patient has undergone medical nutrition therapy (MNT) and lifestyle modification, or (iv) the patient is yet to begin MNT.

Figure 3a shows the country-wide and region-wise trend of estimating the basal insulin initiation dose among HCPs. The figure demonstrates that 77.9% of the HCPs throughout the country calculated the initiating insulin dosage between 0.1 and 0.2 U/kg/day depending on the degree of hyperglycemia. In the scenario of basal only initiation, 45.8% HCPs resorted to fasting and post-meal method for monitoring blood sugar levels post-initiation, and 29.7% HCPs used daily fasting values as a measure to assess the efficacy of the insulin initiation dose (Fig. 3b). On the contrary, Fig. 3c depicts that only 3% HCPs used daily fasting values as a measure to assess the efficacy of the insulin initiation dose for premix or basal bolus or basal plus or basal + glucagon-like peptide 1 (Basal + GLP1) initiation. Most of the HCPs (47.1%) from the study still preferred the fasting and post-meal method for monitoring blood sugar levels post-initiation. In addition, a sizeable lot of HCPs (22.1%) also preferred to use the 5-point scale method as a measure to assess the efficacy of the insulin initiation dose

Table 2 Clinical characteristics. The table documents physician survey report on the clinical characteristics that are factored in while initiating insulin

Variable	Pan-India (*n*=367)	North (*n*=57)	South (*n*=151)	East (*n*=54)	West (*n*=66)	Central (*n*=39)
Most common indication for initiating insulin in T2DM patients, *n* (%)						
Acute hyperglycemia, DKA/hyperglycemic-hyperosmolar state/lactic acidosis	50 (13.62)	7 (12.3)	24 (15.9)	8 (14.8)	9 (13.6)	2 (5.13)
Patients on steroid therapy	1 (0.27)	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)
Indicated for a short period of time in cases of acute illness or surgery, and glucose toxicity	39 (10.63)	4 (7)	21 (13.9)	8 (14.8)	4 (6.1)	2 (5.13)
Pregnancy and lactation	20 (5.45)	2 (3.5)	9 (6)	2 (3.7)	6 (9.1)	1 (2.56)
Patients who fail to achieve glycemic targets with current OADs, or cannot tolerate current OADs, or those who need more flexible therapy	225 (61.58)	41 (71.9)	84 (55.6)	31 (57.4)	42 (63.6)	27 (69.23)
When adequate glycemic control is not obtained, in patients with myocardial infarction, stroke, or decompensated hepatic or renal insufficiency, or those who had major surgery	32 (8.45)	3 (5.3)	13 (8.6)	5 (9.3)	4 (6.1)	7 (17.95)
Number of OADs before initiating insulin therapy, *n* (%)						
Two	55 (15)	5 (8.8)	32 (21.2)	6 (11.1)	6 (9.1)	6 (15.4)
Three	217 (59.1)	36 (63.1)	82 (54.3)	35 (64.8)	40 (60.6)	24 (61.5)
Four	49 (13.4)	11 (19.3)	16 (10.6)	7 (13)	10 (15.15)	5 (12.8)
As a last option after trying all available OADs	46 (12.5)	5 (8.8)	21 (13.9)	6 (11.1)	10 (15.15)	4 (10.3)
Most common type of insulin initiation in T2DM patient, *n* (%)						
Basal only	194 (52.9)	35 (61.4)	66 (43.7)	23 (42.6)	40 (60.6)	30 (76.9)
Premix	123 (33.5)	12 (21.1)	72 (47.8)	20 (37)	17 (25.8)	2 (5.1)
Basal plus	11 (3)	2 (3.5)	4 (2.6)	4 (7.4)	0 (0)	1 (2.6)
Basal bolus	33 (9)	6 (10.5)	7 (4.6)	7 (13)	8 (12.1)	5 (12.8)
Basal + GLP1	6 (1.6)	2 (3.5)	2 (1.3)	0 (0)	1 (1.5)	1 (2.6)
Most common type of insulin initiation in T1DM patient, *n* (%)						
Basal only	16 (4.4)	3 (5.3)	9 (6)	2 (3.7)	1 (1.5)	1 (2.6)
Premix	77 (21)	14 (24.6)	39 (25.8)	12 (22.2)	12 (18.2)	0 (0)
Basal plus	35 (9.5)	2 (3.5)	19 (12.6)	5 (9.3)	8 (12.1)	1 (2.6)
Basal bolus	234 (63.8)	37 (64.9)	82 (54.3)	34 (63)	44 (66.7)	37 (94.9)
Basal + GLP1	5 (1.4)	1 (1.8)	2 (1.3)	1 (1.9)	1 (1.5)	0 (0)
Premix insulin preference, *n* (%)						
Analogue premix	196 (53.4)	33 (57.9)	71 (47)	30 (55.6)	33 (50)	29 (74.4)
Human premix	171 (46.6)	24 (42.1)	80 (53)	24 (44.4)	33 (50)	10 (25.6)
Initiation of insulin therapy in patients with GDM, *n* (%)						
After glibencalmide	6 (1.6)	0 (0)	3 (2)	0 (0)	3 (4.5)	0 (0)
After medical nutrition therapy and lifestyle modification	265 (72.2)	45 (78.9)	105 (69.5)	35 (64.8)	43 (65.2)	37 (94.9)
After metformin	51 (13.9)	6 (10.5)	18 (11.9)	12 (22.2)	15 (22.7)	0 (0)
Before medical nutrition therapy	45 (12.3)	6 (10.5)	25 (16.6)	7 (13)	5 (7.6)	2 (5.1)
Calculating basal insulin initiation dose, *n* (%)						
0.1–0.2 units/kg/day depending on the degree of hyperglycemia	286 (77.9)	43 (75.4)	112 (74.2)	41 (75.9)	56 (84.85)	34 (87.2)
Don't calculate and start at 10 units/day	70 (19.1)	12 (21.1)	34 (22.5)	10 (18.5)	9 (13.64)	5 (12.8)
Less than 8 units/day	11 (3)	2 (3.5)	5 (3.3)	3 (5.6)	1 (1.51)	0 (0)
Frequency of blood sugar monitoring post initiation for initial 2 weeks for basal only therapy, *n* (%)						
5-point scale	32 (8.7)	10 (17.5)	7 (4.6)	6 (11.1)	4 (6.1)	5 (12.8)
7-point scale	7 (1.9)	2 (3.5)	3 (2)	0 (0)	2 (3)	0 (0)
Custom scale	51 (13.9)	9 (15.8)	25 (16.6)	4 (7.4)	12 (18.2)	1 (2.6)
Fasting and post-meal	168 (45.8)	22 (38.6)	68 (45)	26 (48.1)	28 (42.4)	24 (61.5)
Fasting values daily	109 (29.7)	14 (24.6)	48 (31.8)	18 (33.3)	20 (30.3)	9 (23.1)
Frequency of blood sugar monitoring post initiation for initial 2 weeks for premix or basal bolus or basal plus or basal +GLP1 therapy, *n* (%)						
5-point scale	81 (22.1)	15 (26.3)	24 (15.9)	13 (24.1)	12 (18.2)	17 (43.6)
7-point scale	43 (11.7)	9 (15.8)	14 (9.3)	4 (7.4)	11 (16.7)	5 (12.8)

Table 2 (continued)

Variable	Pan-India (*n*=367)	North (*n*=57)	South (*n*=151)	East (*n*=54)	West (*n*=66)	Central (*n*=39)
Custom scale	59 (16.1)	7 (12.3)	27 (17.9)	6 (11.1)	13 (19.7)	6 (15.4)
Fasting and post-meal	173 (47.1)	26 (45.6)	79 (52.3)	29 (53.7)	29 (43.9)	10 (25.6)
Fasting values daily	11 (3)	0 (0)	7 (4.6)	2 (3.7)	1 (1.5)	1 (2.6)
Frequency of titrating the dose of basal insulin in case of basal only therapy after initiation, *n* (%)						
Every 14th day or more	41 (11.2)	1 (1.8)	28 (18.5)	3 (5.6)	5 (7.6)	4 (10.3)
Every 3rd day	208 (56.7)	34 (59.6)	80 (53)	30 (55.6)	37 (56.1)	27 (69.2)
Every week	100 (27.2)	19 (33.3)	39 (25.8)	19 (35.2)	17 (25.8)	6 (15.4)
Everyday	18 (4.9)	3 (5.3)	4 (2.6)	2 (3.7)	7 (10.6)	2 (5.1)
Initiation of insulin in newly diagnosed T2DM patients is a rescue therapy, *n* (%)						
Yes	252 (68.7)	35 (61.4)	98 (64.9)	39 (72.2)	52 (78.8)	28 (71.8)
No	115 (31.3)	22 (38.6)	53 (35.1)	15 (27.8)	14 (21.2)	11 (28.2)

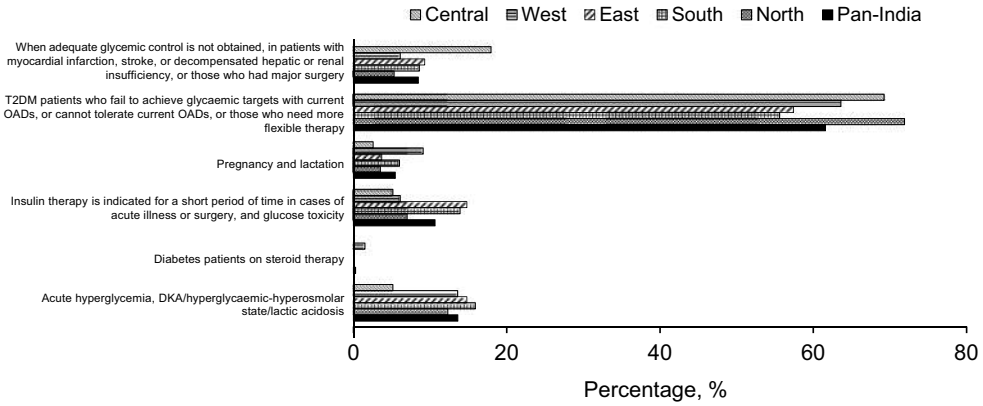

Fig. 1 Indications for initiating insulin in type 2 diabetes mellitus patients

for premix or basal bolus or basal plus or basal + GLP1 initiation. In addition, 56.7% HCPs across the country opted to titrate the dose of basal insulin every third week after initiation in case of basal only therapy. In 68.7% of newly diagnosed cases of T2DM throughout India, initiation of insulin was considered a rescue therapy by HCPs.

Behavioral characteristics

Apart from clinical and care characteristics, the efficacy of insulin initiation to manage glucose levels in T1 and T2DM patients is also dependent on patient acceptability and active compliance to the prescribed regimen. Table 3 lists region-wise and pan-India responses to behavioral characteristics included in the survey. According to the survey, 36.8% of the participating HCPs reported that pan-India, 20–50% of patients refused to adopt insulin therapy. Similar observations were recorded in the region-wise analysis also, where 48.7% of the HCPs in the central region reported a similar trend. Distinctly, 36.8% of HCPs from the northern region and 29.6% of HCPs practicing from the eastern region reported that 50–75% of patients refused to accept insulin therapy.

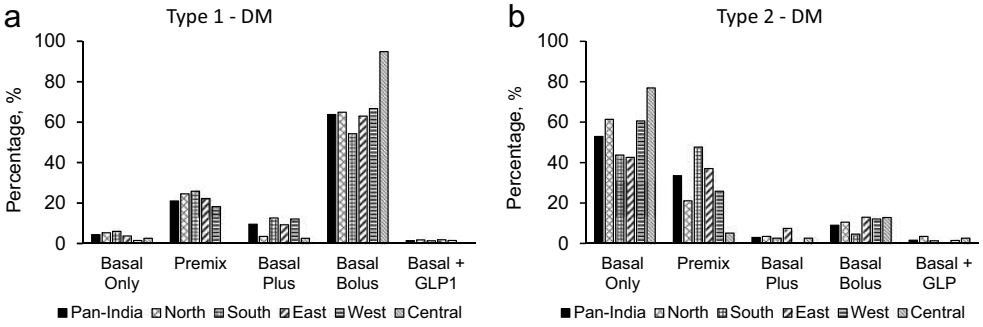

Fig. 2 Comparative analysis between the type of insulin initiated in **a** type 1 and **b** type 2 diabetes mellitus patients

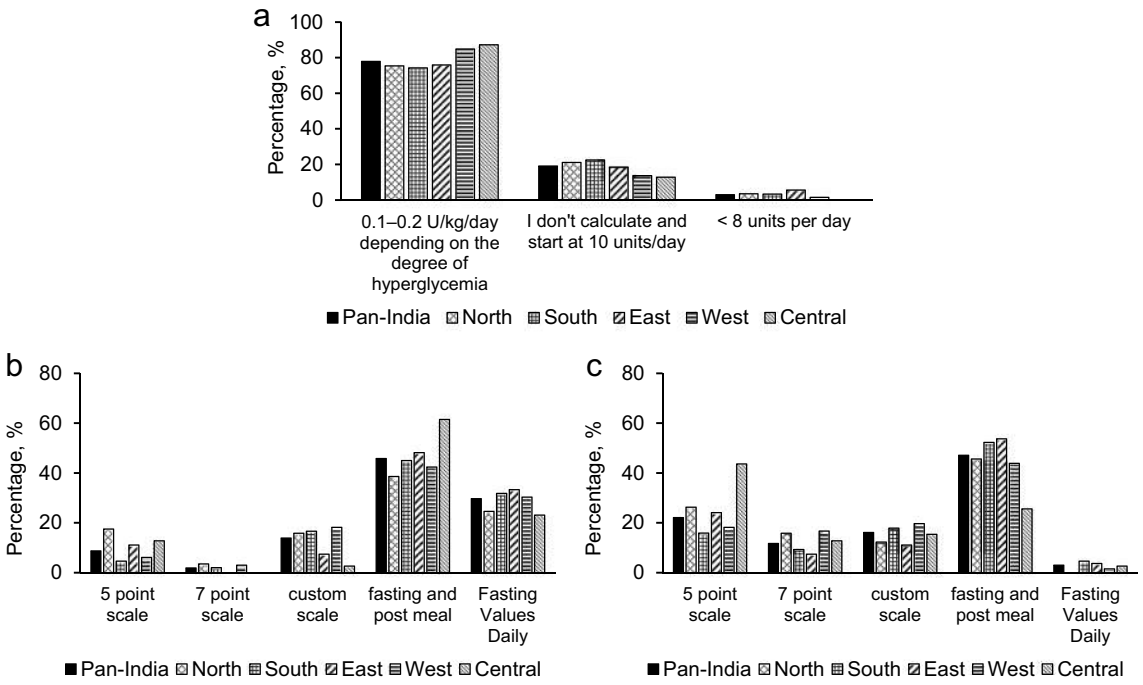

Fig. 3 Country-wide and region-wise analysis of **a** initiation dose of basal insulin, **b** monitoring frequency of blood sugar post initiating basal insulin, and **c** monitoring frequency of blood sugar post initiating premix/basal bolus/basal plus/basal+GLP1 insulin (GLP1, glucagon-like peptide 1)

The study also suggests that 91.6% of HCPs across India conceded to not resorting to insulin initiation to address the psychological fears of patients. Furthermore, 87.5% of the responding practitioners confirmed delaying insulin administration in fear of losing apprehensive/cynical patients. Interestingly, among the responses collected from physicians across India, 76.9% were members of RSSDI and 23.1% were non-members.

Discussion

Significant advancements have occurred in the usage of OADs and several combinations of these OADs are being administered in patients with T2DM to achieve glycemic control through diverse mechanisms of action. However, in most cases, it is observed that these oral hypoglycemic medications fail to provide an optimal glycemic control due to the progressive nature of the disease, necessitating insulin treatment [15]. In this paper, the key factors and concerns that physicians in India consider while initiating insulin therapy in T1 and T2DM patients have been highlighted.

Diabetologists and physicians were the major responders to the survey. Results of the survey indicate that practitioners across the country share a lot of common beliefs about various aspects of insulin initiation practices. For instance, 61.1% of the practitioners agreed that failure to achieve glycemic targets with current OADs or intolerance to current OADs or need for

Table 3 Behavioral characteristics of diabetic patients. The table represents the behavioral data received from practicing physicians who are dealing with patients diagnosed with diabetes derived from the survey report

Variable	Pan-India (*n*=367)	North (*n*=57)	South (*n*=151)	East (*n*=54)	West (*n*=66)	Central (*n*=39)
Delaying insulin initiation due to fear of losing patient, *n* (%)						
Yes	46 (12.5)	4 (7)	19 (12.6)	7 (13)	12 (18.2)	4 (10.3)
No	321 (87.5)	53 (93)	132 (87.4)	47 (87)	54 (81.8)	35 (89.7)
Percentage of patients refusing insulin therapy, *n* (%)						
20–50 %	135 (36.8)	16 (28.1)	60 (39.7)	17 (31.5)	23 (34.8)	19 (48.7)
50–75 %	74 (20.2)	21 (36.8)	24 (15.9)	16 (29.6)	8 (12.1)	5 (12.8)
Less than 20%	119 (32.4)	18 (31.6)	55 (36.4)	14 (25.9)	22 (33.3)	10 (25.6)
More than 75%	39 (10.6)	2 (3.5)	12 (8)	7 (13)	13 (19.7)	5 (12.8)
Using insulin initiation as a tool to fear patients, *n* (%)						
Yes	31 (8.4)	4 (7)	10 (6.6)	2 (3.7)	9 (13.6)	6 (15.4)
No	336 (91.6)	53 (93)	141 (93.4)	52 (96.3)	57 (86.4)	33 (84.6)

a more flexible therapy is the most common indication for initiating insulin in T2DM patients. What is more, 59.6% of HCPs prefer to initiate insulin after three OADs. As per the survey results, 52.4% HCPs consider basal only therapy for insulin initiation in type 2 DM. In cases where HCPs start with premix insulin, 53.2% of them prefer analogue premix insulin. While the American Diabetes Association (ADA) recommends starting basal insulin alone for insulin initiation [16], the International Diabetes Federation (IDF) considers the use of premix insulin apart from basal insulin [17]. In addition, RSSDI and other various regional guidelines recommend basal insulin, premix insulin, or insulin co-formulations for initiating insulin therapy and, thus, are more relevant and allow greater flexibility [18]. Practitioners also prefer biphasic analogue insulins since they can be administered once, twice, or even thrice daily with the benefit of lower risk of hypoglycemia, mealtime flexibility, and better postprandial glycemic (PPG) control compared to biphasic human insulin [19]. Further improvements with premix insulin have led to the development of insulin degludec and insulin aspart (IDegAsp) which offer the benefit of once- or twice-daily dosing with the largest meal(s) of the day.

The survey also revealed that the context of the diverse socio-cultural, economic, and dietary profiles across the country is an important consideration that HCPs consider while deciding on suitable treatment profiles for diabetes management. Another major concern is the reluctance of patients to accept insulin therapy as a measure to control their glycemic levels and further in compliance with the dosing regimen. Despite proper counselling and advising patients about the need for initiating insulin, 36.8% of doctors experienced clinical inertia to initiate insulin therapy in about 20–50% of patients. Furthermore, poor glycemic control is observed in populations with a lack of awareness about their blood glucose levels and those who rely only on diet and exercise regimes for the management of diabetes. Notwithstanding these concerns, 87.5% of the practitioners in the survey responded that they do not delay insulin initiation due to fear of losing patients.

Another factor for concern in the Indian context is the indecision of clinicians to initiate insulinization at the onset of diagnosis. Notably, RSSDI supports insulinization practices throughout India with guidelines on initiating insulin therapy after three oral hypoglycemic agents fail to achieve satisfactory control over blood glucose [18]. Contrary to this, several studies across the globe have shown that in people with newly diagnosed T2DM, early intensive insulin therapy helps in modifying the natural history of diabetes by preserving beta-cell function [20]. The International Diabetes Federation (IDF) global guidelines for diabetes management recommend that insulin therapy should be individualized for every patient according to their glycemic profile, presence of comorbidities, the risk of hypoglycemia, and after failing to achieve glycemic targets with single-, dual-, or triple-oral therapy. Nevertheless, it is a widespread observance across the country that clinicians hold up initiation and intensification of insulin due to cost, fear of adverse effects, and sub-optimal knowledge about insulin treatment.

The findings of this survey also resonate with the outcomes of the DiabCare India study [1]. As per the DiabCare India study, 93.2% of patients with diabetes in India are found to be on OADs while 35.2% are on insulin (with or without OADs). The study also reports that premix insulin is prescribed for most patients followed by prandial insulin (39.4%) and basal bolus insulin (19.4%). As per the Diabetes in Pregnancy Study group India (DIPSI) guidelines, insulin is considered the standard treatment for GDM cases when patients fail to achieve adequate glycemic levels even after 2 weeks of MNT [21]. In the survey also, 72.4% of the responses from HCPs indicated their preference to start insulin therapy after the MNT and lifestyle modification.

A limitation of this survey is that the data were self-reported and may vary from the actual insulin initiation practices of the survey participants. We also admit that the responses given by 367 practitioners are not sufficient to generalize the results in a large country like India. Nevertheless, despite these limitations, the insights gained through this survey on the insulin initiation practices among Indian physicians can aid in outlining frameworks for future research on the use of insulin to optimize long-term glycemic control in diabetic patients.

In conclusion, the results of the survey indicate the issue of clinical inertia and lack of awareness to initiate insulin for the proper and long-term management of diabetes, from both the economic and healthcare perspectives. This calls for urgent attention from policymakers and healthcare professionals on the need to review the existing diabetes care and insulinization initiation practices in India. A key milestone would be spreading awareness among the population to accept insulin as a means to manage their glycemic levels and avoid diabetes-related complications in the long run.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-022-01123-x.

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Declarations

Conflict of interest Dr. Nishtha Manish Singh is also a part of the scientific department at Neovation Consultancy Services Pte. Ltd., Singapore.

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ORIGINAL ARTICLE

Value of neutrophil/lymphocyte ratio in the diagnosis of diabetic neuropathy

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Abstract

Background Peripheral diabetic neuropathy (PDN) had been demonstrated as a chronic inflammation state and one of the most common complications of type 2 diabetes mellitus (T2DM). Neutrophil-to-lymphocyte ratio (NLR) is a novel marker to reflect many kinds of chronic inflammation disease including diabetes. We aim to evaluate the association between NLR and PDN and to determine whether NLR could be a new indicator of PDN in T2DM.

Methods Hospital records of the patients who underwent electroneuromyography studies with the diagnosis of T2DM in the Neurology Outpatient Clinic between 01/01/2018 and 01/04/2021 were divided into two groups as those with normal results and those with polyneuropathy. The NLR was calculated from the hemogram tests.

Results Eighty-nine (52.7%) normal and 80 (47.3%) PDN patients included in the study, of them 77 (45.6%) were male and 92 (54.4%) were female. The mean age of the patients was 58.92±13.88 years. According to the records examined, the mean NLR value was significantly higher in patients with PDN (2.70±1.99) than in those with normal results (1.98±0.80). According to the ROC analysis, the sensitivity is 0.875 and the specificity is 0.292 for 1.46, which is determined as the optimal cut-off value for the NLR value in the diagnosis of PDN.

Conclusion The results of our study have shown that there was a significant correlation between NLR and PDN, implying that inflammation and endothelial dysfunction could be an integral part of PDN. NLR was significantly and independently raised in patients with T2DM.

Keywords Diabetes · Peripheral diabetic neuropathy · Neutrophil-to-lymphocyte ratio · ROC analysis

Background

Peripheral neuropathy is a term used to describe general diseases of the nervous system and is seen with motor, sensory and autonomic symptoms. Approximately 50% of all polyneuropathies are associated with pain. Peripheral diabetic neuropathy (PDN) is a common serious complication of diabetes and negatively affects the daily lives of patients.

Diabetes is an increasingly common disease. The World Health Organization (WHO) estimates that by 2025 the total number of diabetics will reach 300 million. Its prevalence is approximately 0.3–0.5%. Type 2 diabetes mellitus (DM) is usually observed over the age of 40. It progresses with insulin deficiency and insulin resistance in peripheral tissues. The prevalence of diabetes mellitus varies with age [1, 2].

Complications begin in the first years following the diagnosis of diabetes or patients are affected by complications when the diagnosis is made. Although many factors cause the development of PDN, the most effective method in the development of complications and prognosis is to keep the blood glucose level under good control [3, 4].

PDN may present clinically as neuropathic pain, trophic changes, motor symptoms, and autonomic dysfunction. Although glycemic control reduces the risk of neuropathy in diabetic patients, unfortunately, there is no effective treatment for diabetic neuropathy yet. Nerve damage in PDN occurs as a result of metabolic factors, oxidative stress, ischemic factors, and inflammation. Neuroinflammation is a physiological process necessary for regeneration and healing. As a result of deterioration of neuroinflammation, chronic pain occurs [5, 6].

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Neutrophil-to-lymphocyte ratio (NLR) is an inexpensive and easily calculated index that correlates with the prognosis of systemic inflammatory diseases. It can be used especially in inflammatory, cardiovascular, and cancer diseases [7, 8].

PDN is a common complication of diabetes that may be associated with inflammation and vascular diseases. PDN is a disease that significantly impairs quality of life and prevents activities of daily living. Increased levels of peripheral inflammation may play a role in the pathogenesis of PDN. Differential diagnosis of this disease involves some difficulties. NLR and similar markers are easily accessible parameters and can be used in differential diagnosis and can guide clinicians in diagnosis. In this study, the neutrophil-to-lymphocyte ratios of patients with proven PDN by electroneurophysiological tests and the use of NLR ratio in the differential diagnosis were clarified by comparing them in patients with diabetes and without neuropathy.

Materials and methods

The study was carried out on the patient registration system data of Çanakkale Onsekiz Mart University Hospital. Ethics committee approval was obtained for the study from Çanakkale Onsekiz Mart University Ethics Committee for Clinical Studies with decision number 05-19 dated May 06, 2021. The study population consisted of the patients included in the hospital registration system, and the study sample consisted of the records selected from here within the study inclusion criteria.

Patient's records of who underwent electroneuromyography (ENMG) with the diagnosis of DM in the Neurology Outpatient Clinic of Çanakkale Onsekiz Mart University Hospital between January 2018 and April 2021 were collected from the patient registry system. All records available between the specified dates were included in the study. The study method did not involve any patient contact.

The NLR was calculated from the hemogram test results. The oldest hemogram test result was taken if more than one test present. Records of patients with diseases known to seriously impair hemogram parameters (oncological diseases, hematological diseases, acute vascular diseases, end-stage renal disease, inflammatory diseases (e.g., ankylosing spondylitis, ulcerative colitis), and acute infections) were excluded. Hemogram measurements were studied using the Coulter method on the hospital's Beckman Coulter DXH800 device.

PDN was diagnosed according to nerve conduction study (NCS) recordings done as part of ENMG performed with a Nihon-Kohden device (NihonKohden-Neuropack®) and interpreted by an experienced neurologist (first author). NCS was performed on three extremities of each subject including motor components of the peroneal, posterior tibial, median, and ulnar nerves and sensory components of the sural, median, and ulnar nerves; nerve conduction velocities; distal latencies; and amplitudes were recorded. Demyelinating neuropathy was diagnosed in prolonged distal motor latency, slowed conduction velocity, conduction blocks, and prolonged or absent F-wave latency while axonal neuropathy was diagnosed when low or loss of motor and sensory action potential was detected.

Patients with normal or mixed-type sensorimotor polyneuropathy in the NCS results were included in the study; other subtypes of PDN and mononeuropathy were excluded. Patients were divided into two groups according to their NCS as PDN and normal results.

NCS results in 89 (52.7%) were normal. Out of 90 NCS reflecting pathological results, 74 (82.2%) were diffuse mixed-type sensorimotor polyneuropathy, 6 (6.7%) were mixed-type sensorimotor polyneuropathy in the lower extremities, 7 (7.8%) were carpal tunnel syndrome, 1 (1.1%) was sensory polyneuropathy, 1 (1.1%) was demyelinating polyneuropathy, and 1 (1.1%) was ulnar neuropathy. When all NCS results were evaluated, it was determined that there were 80 (47.3%) patients with mixed-type sensorimotor polyneuropathy as a complication of DM. Patients with mononeuropathy and subtypes of PDN other than mixed-type sensorimotor polyneuropathy were excluded from the study and the study was conducted on 169 outcomes.

Statistical analysis

Collected data were digitalized and corrected; descriptive information is presented as the frequencies and percentages for categorical data, and with mean and standard deviation for ordinal data. Since the sample number was larger than 30, the normal distribution assumption of parametric tests was ignored based on the central limit theorem. In the evaluation of the strength of the correlations, $r < 0.30$ was classified as weak, $0.30 \leq r < 0.50$ moderate, and $r \geq 0.50$ strong. Chi-square, Student t, and Pearson correlation tests were used for statistical analysis. When the expected value was less than 5, Fisher's exact test result was reported. Test constants and absolute p values are presented for all analyses and $p < 0.05$ was accepted as the general significance limit. ROC analysis was performed to determine the diagnostic power of the NLR value for PDN. The optimal cut-off value was selected and reported in the ROC curve obtained.

Results

Of the 169 recordings included in the study, 89 (52.7%) of the NCS results were normal and 80 (47.3%) were mixed-type sensorimotor PDN. Of the 169 records included in the study, 77 (45.6%) were male and 92 (54.4%) were female patients. The mean age of the patients was 59.05 ± 14.02 (minimum 20 and maximum 87). The mean age of men (58.92 ± 13.88) was

not significantly different from that of women (59.15 ± 14.20) ($t = 0.106$; $p = 0.916$).

The rate of women with PDN (38.0%) was significantly lower than that of men (58.4%) ($X^2 = 6,996$; $p = 0.008$). The mean age of those with PDN (62.14 ± 12.79) was significantly higher than that of the normal (56.27 ± 14.55) ($t = 2.771$; $p = 0.006$).

According to the records examined, the mean neutrophil count in mm^3 blood was 4.80 ± 2.09, and the lymphocyte count was 2.33 ± 0.83. The mean NLR value was 2.32 ± 1.53. While the mean lymphocyte count of women (2.17 ± 0.75) was higher than that of men (2.52 ± 0.88) ($t = 2.801$; $p = 0.006$), there was no significant difference between the sexes in terms of mean neutrophil counts and NLR ratio ($t = 0.034$, $p = 0.973$ and $t = 0.968$, $p = 0.335$ respectively). While there was a weak negative correlation between age and mean lymphocyte count ($r = -0.152$; $p = 0.049$), there was no significant correlation with neutrophil count and NLR ($r = 0.002$; $p = 0.975$, $r = 0.082$; $p = 0.287$, respectively).

Table 1 shows the neutrophil count, lymphocyte count, and NLR values in patients with PDN and normal EMG. The appearance of NLR values in patients with normal NCS results and PDN is presented in Figure 1.

The ROC analysis curve for the comparison of the NLR values of those with PDN and those with normal NCS results is presented in Figure 2. According to the results of the analysis, the area under the curve was calculated as 0.593 (95% confidence interval 0.508–0.679) (standard error = 0.044, $P = 0.036$). According to the results of the analysis, the optimal cut-off value for the NLR value in the diagnosis of PDN was determined as 1.46, and the sensitivity for this value was 0.875 and the specificity was 0.292. For the cut-off value of 2.485, the sensitivity was 0.338 and the specificity was 0.775.

Discussion

Involvement of the peripheral nervous system in diabetic patients affects the quality of life. Diabetes can affect various parts of the nervous system. PDN is the most common peripheral nervous system complication and defined as the presence of symptoms of peripheral nerve dysfunction in diabetic patients after excluding other causes of neuropathy [9]. The diagnosis of PDN is recommended on the basis of neuropathic symptoms, signs, and nerve conduction studies, and there is no gold standard [10].

Inflammatory processes play a key role in DM like other chronic diseases including cardiovascular disease, cancer, and chronic kidney disease [11]. Peripheral nerve inflammation leads to oxidative stress, and increased reactive oxygen concentrations have been associated with the development of microvascular complications of diabetes, including neuropathy. Total antioxidant levels were low and total oxidative status increased in diabetic patients with neuropathy [12, 13]. In a prospective study, biomarkers of inflammation were associated with the onset and progression of neuropathy in an elderly population with diabetes [14].

Chronic inflammation accompanying metabolic dysfunction in type 2 DM supports the development and acceleration of micro- and macro-angiopathic complications [15]. Inflammatory molecules (such as adipokines, chemokines, adhesion molecules, and cytokines) and endothelial dysfunction play a role in disease processes [16].

NLR, a new marker of chronic inflammation, reflects the balance of two interconnected components of the immune system. The first of these is neutrophils, which form the first line of defense as active nonspecific inflammatory mediators, and the other is lymphocytes, which are the regulatory or protective component of inflammation [17]. It has been demonstrated that NLR calculated from blood cell counts can be used as an indicator of systemic inflammation [18]. Systemic inflammation reflected by NLR has been associated with chronic diseases such as hypertension and diabetes [19]. In addition to being associated with glucose intolerance and insulin resistance, NLR has been shown to be used as a prognostic marker for macro- and microvascular complications in diabetic patients [20].

Inflammation has a significant impact on the development and progression of PDN [21]. Inflammatory molecules and endothelial dysfunction play an important role in the PDN

Table 1 The status of neutrophil and lymphocyte counts and NLR values in those with normal NCS results and PDN

	EMG result		
	Normal ($n = 89$)	PDN ($n = 80$)	Analyses*
Neutrophil count (per mm^3)	4.48 ± 1.53	5.16 ± 2.55	$t = 2.133$; $p = 0.034$
Lymphocyte count (per mm^3)	2.46 ± 0.85	2.18 ± 0.79	$t = 2.177$; $p = 0.031$
NLR value	1.98 ± 0.80	2.70 ± 1.99	$t = 3.145$; $p = 0.002$

*Independent samples *t* test

NLR neutrophil-to-lymphocyte ratio, *NCS* nerve conduction studies, *PDN* peripheral diabetic neuropathy

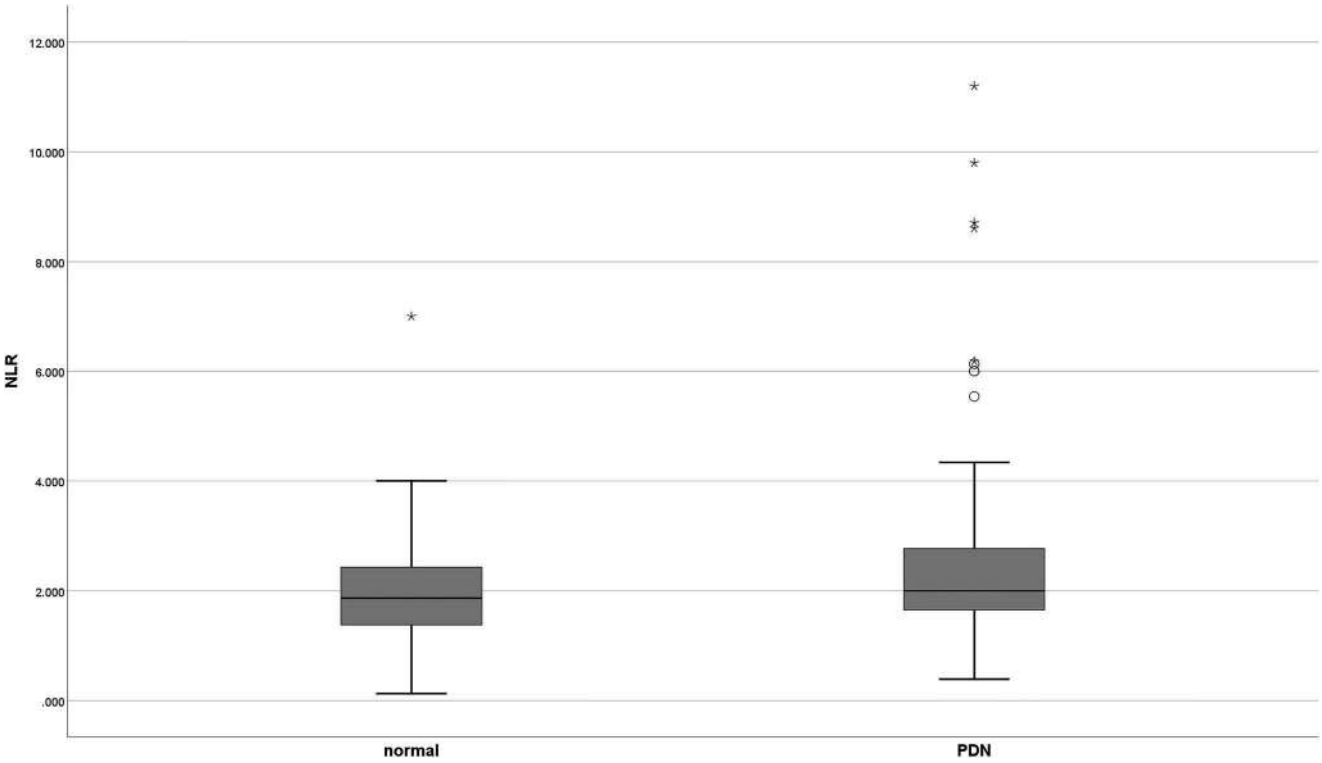

Fig. 1 Neutrophil-to-lymphocyte ratio (NLR) values in patients with peripheral diabetic neuropathy (PDN) and normal NCS results

settings [22]. NLR has also been proposed as a predictor to evaluate the development of microvascular complications of diabetes. Ulu et al. showed that NLR is a reliable prognostic marker for the presence and severity of diabetic retinopathy [23] and a predictive and prognostic marker for sensorineural hearing loss [24].

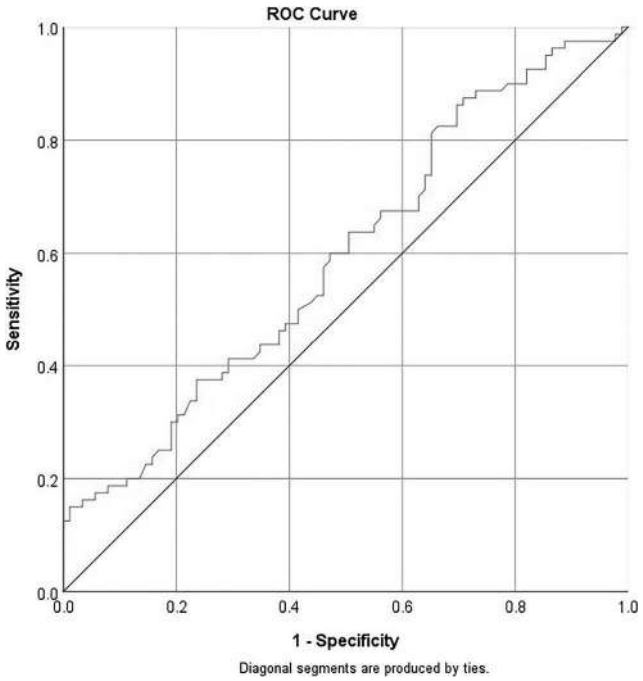

Fig. 2 ROC curve for the comparison of neutrophil-to-lymphocyte ratio values of those with peripheral diabetic neuropathy and normal NCS results

In our study, we investigated the relationship between NLR and PDN in patients with electroneurophysiologically detectable sensorimotor polyneuropathy. There are studies investigating the relationship between PDN and NLR but this study focused on a specific subtype of diabetic neuropathy. We concluded that NLR has a significant predictive value and can be used as a prognostic marker for diabetic mixed-type sensorimotor polyneuropathy.

In a recent study, T1 and T2 DM patients were followed up for 18 months and newly developed PDN cases were separated and examined [25]. According to the results of the study, NLR and platelet-to-lymphocyte ratio (PLR) for T1DM and NLR for T2DM were significant markers for the development of PDN. The sensitivity for NLR at a cut-off value of 2.485 was calculated as 0.380 and specificity 0.790 for demonstrating the development of PDN in T2DM.

Our results have very close sensitivity (0.338) and specificity (0.775) values with the cut-off value (2.485) reported in this study. Although the figures have not been reported, it is observed that very close values have been reached in the ROC graph of this study for the optimal cut-off value (1.46) that we suggest according to our study results. When the results are interpreted together, it can be concluded that the NLR results between the two specified cut-off values will be less reliable in clinical decision-making.

Although high diagnostic values of NLR values in other diabetic complications such as nephropathy and retinopathy have been reported in various studies, it should be kept in mind that cut-off values and diagnostic powers will be different for each clinical situation.

The primary limitation of our study is that it was conducted retrospectively. However, the effects of this will not be very serious because the diagnoses of the patients were made by electroneurophysiological tests and the hemogram values performed at the diagnosis were used. In fact, unlike other vascular complications of diabetes, it is difficult to clearly determine when PDN begins. Another limitation is that only large fiber neuropathies are included. Nerve conduction studies, which are widely used for peripheral neuropathies, are primarily based on large nerve functions and are often found to be normal in small fiber neuropathies. Finally, the clinical signs and symptoms of the patients were not evaluated in our study. In accordance with the aim and method of the study, only electroneurophysiological diagnosis was focused. The mechanism of formation of neuropathic pain, which is the most important symptom, differs from neuropathy and its presence or absence is not correlated with neuropathy. Although other screening tests based on symptoms and findings may aid in the diagnosis of clinical neuropathy, they will not be of additional benefit for patients with a definitive electroneurophysiological diagnosis.

Conclusion

The results of our study showed that there is a significant correlation between NLR and PDN. NLR can be considered as a predictor of PDN and a prognostic risk marker. NLR is an easy parameter to calculate using blood cell counts. This test is simple, inexpensive, and routinely performed. NLR can be an alternative to other expensive inflammatory markers when laboratory facilities and financial constraints exist. More research with prospective design should be conducted on the role of NLR as a marker of inflammation and a risk factor for PDN.

Author contribution All authors contributed to the study conception and design, material preparation, data collection and analysis, and draft writing of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval Approval was obtained from the Çanakkale Onsekiz Mart University Ethics Committee for Clinical Studies with decision number 05-19 dated May 06, 2021. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

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ORIGINAL ARTICLE

Serum glucose, a cost-effective alternate of plasma glucose in diagnosing and monitoring diabetes mellitus

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Abstract

Background Measurement of venous plasma glucose concentration (P-Glucose) requires preanalytical precautions: rapid cooling, rapid centrifugation, and using tubes with enzyme inhibitors. A special routine for measuring a biomarker that is critical and frequent in metabolic control is logistically demanding and expensive. We revisit and quantify the diagnostic outcome of using venous serum glucose concentration (S-Glucose) to diagnose diabetes mellitus (DM), using glycated hemoglobin (B-HbA_{1c}) as the reference procedure for diagnosis.

Methods Data from 301 participants, with simultaneous measurements of B-HbA_{1c}, fasting S-Glucose and P-Glucose, without diabetes medication or established diagnosis were included. The WHO definition of DM as a B-HbA_{1c} value ≥ 47.5 mmol/mol (6.5%) was used to define DM. The optimal concentration cutoff for S-Glucose was identified using the receiver operating characteristic curve and the cumulative data analysis tools. The diagnostic performance was evaluated by the diagnostic sensitivity, specificity, and the positive likelihood ratio of the S-Glucose measurements.

Results The correlation between S-Glucose and P-Glucose was 0.999. S-Glucose had a diagnostic sensitivity and specificity of 91% and 99% and P-Glucose of 97% and 95%, respectively, to diagnose DM when a cutoff value of 6.9 mmol/L (125 mg/dL) was used and in relation to the diagnosis established by B-HbA_{1c}.

Conclusion The diagnostic sensitivity and specificity of S-Glucose equals those of P-Glucose when compared to the WHO B-HbA_{1c} criteria. In comparison, S-Glucose instead of P-Glucose saves costs, optimizes the use of the patient sample, and improves the logistics of samples and reagents.

Keywords Plasma glucose · Serum glucose · Glycated hemoglobin (B-HbA_{1c}) · Receiver operating characteristic analysis (ROC) · Cumulative data analysis (CDA)

Introduction

The cardinal signs and symptoms of diabetes mellitus (DM) are laid down already in the name "diabetes" referring to thirst and polyurine (Greek "siphone") and "mellitus" to the excessive sweetness of blood and urine. In ancient times, the disease was diagnosed by recognizing the excretion of glucose in urine which, anecdotally, is said to have been discovered by urine attracting insects or the physician tasting the urine.

In a recent newsletter, the World Health Organization (WHO) estimated that the global diabetes load reached 422 million in 2014 and between 2000 and 2016; there was a 5% increase in premature mortality from diabetes [1]. The WHO and professional organizations, e.g., American Diabetes Association (ADA), have issued recommendations to improve and standardize the diagnosis of DM. In 2009, an International Expert Committee appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation concluded that a cutoff point of B-HbA_{1c} =47.5 mmol/mol (6.5%) should be used to diagnose diabetes [2] and the WHO supported this use of B-HbA_{1c} and cutoff for diagnosing DM in 2011.

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Dedicated instruments are available for measuring capillary "blood glucose," some with algorithms to estimate a corresponding P-Glucose. These instruments are designed for primary health care and personal use; however, in many cases, their use in routine health care is prohibited by high costs of instruments and reagents. High productivity instruments reduce costs of glucose measurements in plasma or serum. Particularly, the preanalytical uncertainty is less in professionally collected venous samples than in capillary samples and is therefore preferred. Dedicated instruments and reagents that can be used in primary health care have also been developed for the measurement of B-HbA_{1c}. These are relatively expensive and not universally available. B-HbA_{1c} can be measured in EDTA, EDTA-fluoride, and buffered citrate tubes [3], i.e., the same tubes used for P-Glucose measurements, and methods have been developed to measure B-HbA_{1c} from blood spots applied to paper [4]. In areas where hemoglobinopathies and anemia are abundant, B-HbA_{1c} needs to be measured with special care.

Glucose is rapidly metabolized in blood, mainly by enzyme systems in the corpuscles. The recent ADA guideline therefore recommends that the glucose concentration is measured in venous plasma (P-Glucose) that has been collected in heparin-coated tubes containing a suitable glycolysis inhibitor, usually sodium fluoride (NaF) alone or in combination with a citrate buffer [3]. Glycolysis can also be slowed down or partially inhibited by rapidly cooling the sample and storing it on ice until measured; in fact, this is the first choice according to the American Association of Clinical Chemistry (AACC)-ADA recommendation [5]. S-Glucose as the marker for DM has been frequently used in large population studies [6] and many other studies [7]. Therefore, the experience indicates that it may not always be justified to limit the sample to plasma; in practical work, considering all attached uncertainties using S-Glucose would not jeopardize the management of DM.

Multiple types of tubes increase preanalytical costs and challenge the logistics. Since long, the most commonly used inhibitor is NaF although it has been challenged [8, 9], inter alia, because there is a delay of about 30 min before the inhibitor takes effect. It is therefore reasonable to assume that the glucose concentration in serum and plasma will be largely identical within this time frame. When the corpuscles are removed, the glycolysis ceases. We recently demonstrated that if serum is separated by centrifugation within 30 min, measurements of S-Glucose are not clinically different from those using NaF inhibited plasma for up to 4 h [10]. This is an important finding particularly for clinical settings where preanalytical costs and logistics are major concerns; an extra benefit of using serum for glucose measurements is that other quantities can be measured in the same sample. In the present report, we take a step further by testing and quantifying the diagnostic outcome of measuring S-Glucose and P-Glucose with a view to recommend a cutoff for S-Glucose. The diagnostic cutoff was calibrated to the WHO-recommended concentration of B-HbA_{1c} for diagnosis of DM. We also demonstrate the use of receiver operating characteristic (ROC) curve and cumulative data analysis (CDA) plots to establish critical decision concentrations.

Materials and methods

Subjects

A cross-sectional study was designed enrolling 301 individuals attending Samyak Diagnostic Pvt. Ltd. in Kathmandu, Nepal, for fasting blood glucose and B-HbA_{1c} tests to confirm an alleged diagnosis of diabetes, between March 2021 and July 2021. Subjects were excluded if they were on diabetes medication. Women and men without age discrimination were included. Participants with a B-HbA_{1c} value of $\geq$ 47.5 mmol/mol (n=147) were identified as diabetic, leaving 154 non-diabetics.

Ethical approval for this study was obtained from the Nepal Health Research Council (protocol number-220/2021 P) and a written consent was obtained from each participant in the study.

Methods

S-Glucose, P-Glucose, and B-HbA_{1c} were measured for each participant. Venous blood was drawn in one NaF/Na_2EDTA tube for plasma (BD Vacutainer sodium fluoride/sodium EDTA 13 × 75 mm, 2 mL), one serum separator tube for serum (BD Vacutainer serum separator tube (SST) 13 × 100 mm, 5 mL), and one EDTA tube for B-HbA_{1c} analysis (EDTA.K2 BD Vacutainer 13 × 75 mm tubes, 2 mL). All venipunctures were carried out between 7 am and 10 am to obtain fasting samples. Visibly lipemic, icteric, or hemolyzed samples were not included in the study.

Serum samples were allowed to clot for 20 min at room temperature (26.0 °C, interval 23.6–28.6 °C) and serum and plasma samples were centrifuged at 1600 ×g for 10 min (Remi Neya4 Remi Elektrotechnik Ltd., India) within 30 min. The P-Glucose and S-Glucose concentrations were determined within 2 h after centrifugation.

Paired specimens (serum and plasma) from each participant were analyzed using the same lot of reagent, eliminating any lot-to-lot variability of the results. The glucose concentration was determined spectrophotometrically using Randox Imola auto-analyzer (Randox Laboratories Limited, UK) by a glucose oxidase peroxidase method.

B-HbA_{1c} was measured by high-pressure liquid chromatography (HPLC) (Bio-Rad Variant II, Richmond, CA, USA). Samples with chromatogram indicating Hb variant were excluded from this study to rule out the possibility of false low or high B-HbA_{1c}. The internal quality control system used two levels of control materials and were conducted by qualified technical personnel and properly documented.

For this study, in accordance with the guidelines set forth by the AACC and ADA, diabetes was defined as patients having a B-$HbA_{1c} \geq 48$ mmol/mol (6.5%) [8].Consequently, we identified diabetics in the cohort as individuals fulfilling this criterion. This allowed estimating the common Bayesian characteristics of a decision model for S-Glucose and P-Glucose, i.e., diagnostic sensitivity (Sn), specificity (Sp), positive likelihood ratio (LR(+)), and area under the ROC curve (AUC).

Statistical analysis

Normality was tested by the Kolmogorov-Smirnov test. The difference between the S-Glucose and P-Glucose results was evaluated pairwise by the Wilcoxon signed rank test. < 0.05 was considered statistically significant.

Regression analysis to examine the relation between B-HbA_{1c} and P-Glucose and S-Glucose was done using the Association of Clinical Biochemistry and Laboratory Medicine spreadsheet [11, 12]. The diagnostic performance of glucose for different cutoffs was estimated from the CDA graphs of P-Glucose and S-Glucose [13, 14]. The 95% confidence intervals for Sn and Sp were calculated using the Copper-Pearson exact procedure.

Results

The median age of the 301 participants was 47 (38–54) years and 165 (54%) participants were males. The results of the glucose measurements were not normally distributed (Fig. 1), the right skewness confirms the presence of diseased individuals in the cohort.

The correlation coefficient (r) between S-Glucose and P-Glucose was 0.999. There was a statistically significant difference between the paired results. The average difference (P-Glucose − S-Glucose) in the entire cohort was 0.24±0.19 mmol/L (4.3±3.4 mg/dL), whereas in the medically critical interval, 6.1–7.8 mmol/L (110–140 mg/dL), the P-Glucose concentration was 0.19±0.13 mmol/L (3.4 ±2.3 mg/dL) higher than S-Glucose concentration, i.e., 2.8%, based on the 61 samples in the interval (Fig. 2). A slope of 0.97 and an intercept of 0.66 explain the increasing difference between the observations.

The difference graph, Fig. 3, details the differences between observations.

The diagnostic performance was illustrated in a ROC curve [13], which displays the relation between Sn and 1-Sp at all possible decision points and is a conventional model to describe the performance of a diagnostic test. The performance can be described in terms of the AUC; anything larger than 0.5 would be theoretically useful. A disadvantage of the ROC curve is that it does not allow direct identification of the quantity value corresponding to a given point on the ROC curve. Important quantities in optimizing a test performance are the Sn, Sp, and positive likelihood ratio, LR (+), at the various concentrations.

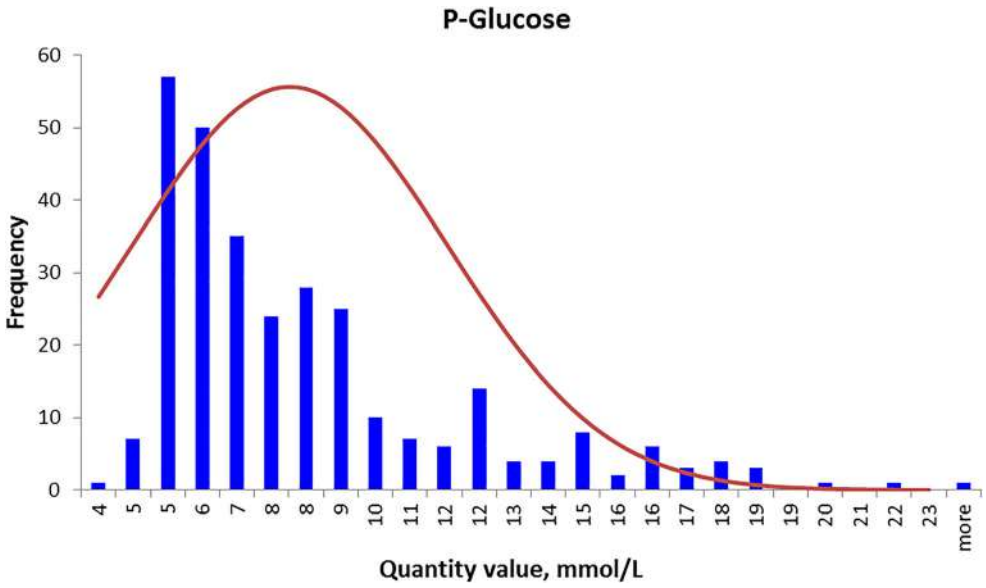

Fig. 1 Distribution of results by P-Glucose. The superimposed normal frequency curve was calculated from the mean and standard deviation of the skewed data

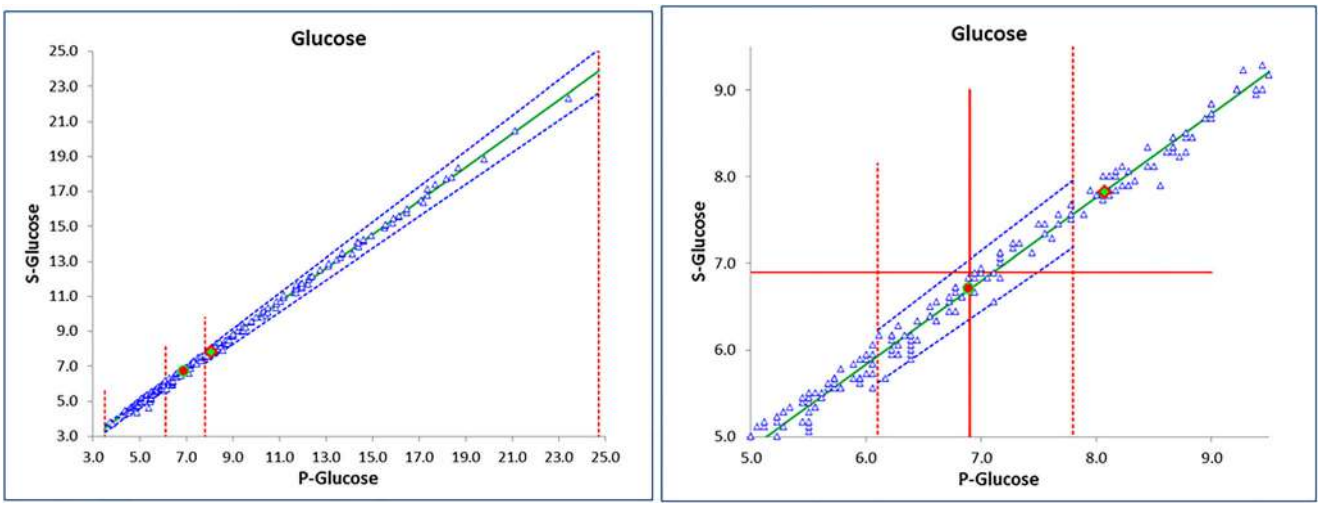

Fig. 2 Comparison between S-Glucose and P-Glucose. The regression line is indicated. The right panel shows the clinically critical interval (6.1–7.8 mmol/L) and the suggested decision point. The oblique dotted lines show the regression line ± 5%, which corresponds to the "A-zone" of the Clark error grid [15]. The accepted difference, also known as the A-zone in the Clark error grid used by the Food and Drug Administration (FDA) to set specifications for point-of care glucometers, is ±5% of the regression function and the patient samples were well within this interval

A graph displaying the relation between these three critical quantities and the quantity value (decision value) is the CDA graph which is automatically generated in the used software [12] (Fig. 4 and Table 1).

A decision value, or cutoff value, corresponding to the optimal LR(+) was 7.2 mmol/L (130 mg/dL) for both markers (Fig. 4). However, this cutoff would generate only a single observation of false positives and thus be associated with a large uncertainty and the estimated specificity almost 100%. It is therefore reasonable to search a pragmatic cutoff and the maximum Youden index (*Y*=Sn+Sp-1) is often used if the clinical values of Sn and Sp are of equal concern. The ROC analyses indicate a maximal Youden index of 7.0 mmol/L (126 mg/dL) and 6.8 mmol/L (124 mg/dL) for P-Glucose and S-Glucose, respectively. The average coincides with the WHO recommendation; i.e., a cutoff of 6.9 mmol/L (125 mg/dL) would be feasible.

The correlation between S-Glucose and B-HbA_{1c} is shown in Fig. 5 (r=0.949) and in the critical diagnostic interval (5.0 to 8.0%) where r = 0.862, the linear relationship was defined as S-Glucose (mmol/L) =0.98 × HbA_{1c} (%) + 0.50, based on142 observations.

Discussion

Although it is well known that addition of only NaF to blood does not inhibit glycolysis immediately, this procedure has

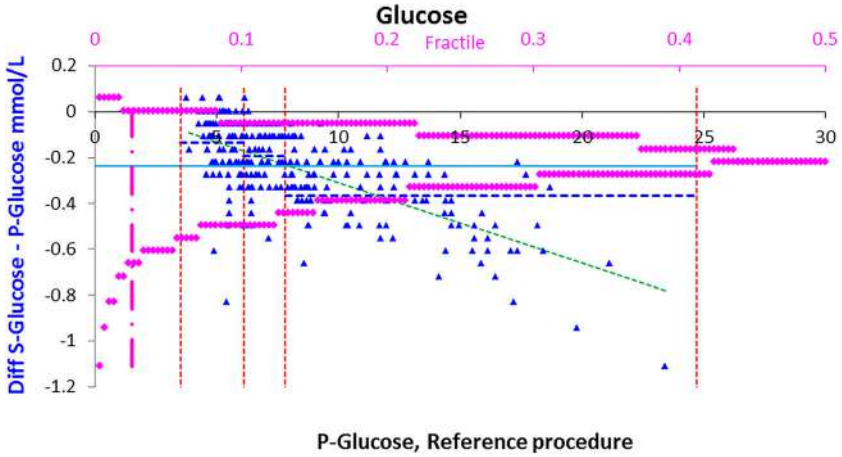

Fig. 3 Difference graph based on the regression between P-Glucose and S-Glucose (Figure 2). The "tilted mountain plot" illustrates the frequency distribution of the differences. The median difference is the peak of the "mountain, also shown by the solid horizontal line." Horizontal dashed lines show the median differences in the partitions. The regression line is that of the differences and its slope is one less than the slope of the regression function between the concentrations. The vertical dash-point line shows the 2.5 percentile, i.e., observations to the left of this line represent 5% of the cohort [12]

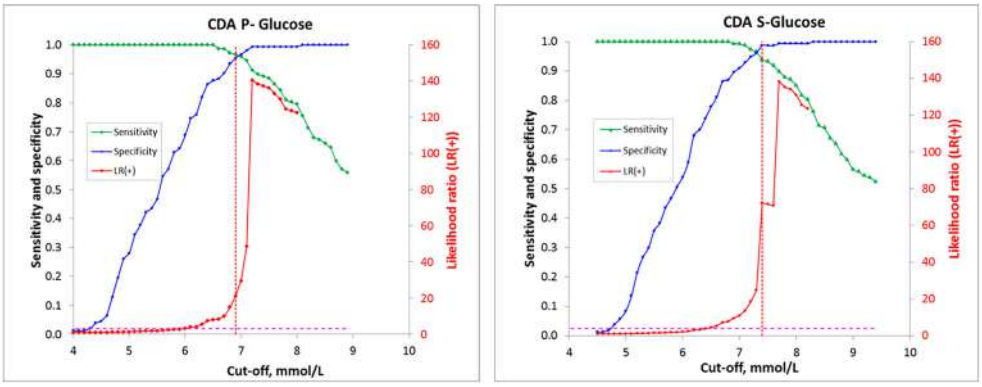

Fig. 4 CDA graphs showing the sensitivity (increasing), specificity (decreasing), and LR(+) (open circles) for P-Glucose (left panel) and S-Glucose. The illustrated cutoff is 6.9 mmol/L for both measurands

become widespread. Many laboratories and clinics recommend using buffered NaF which inhibits glycolysis in the beginning of the process and therefore an immediate inhibition. Both recommendations require special collecting procedures or tubes which are costly and not always available. We have therefore revisited measuring S-Glucose as the primary biomarker for DM. We hypothesize that the procedure we recently described [10], i.e., serum, separated soon after drawing and the S-Glucose measured within a given time would provide information that serves the clinical need for diagnosis and monitoring of DM. If validated, it would reduce costs for keeping and distributing multiple kinds of tubes, simplify logistics, and reduce sampling time and the amount of blood taken. The importance of a rational and optimized measurement procedure, fit-for-purpose, cannot be overemphasized.

The Executive Committee of the ADA issued a report including recommendations for analytical performance of B-HbA_{1c} as the method applied to diagnose diabetes with a discriminatory point of 6.5% DCCT (48 mmol/mol IFCC) [2]. International standardization and harmonization of B-HbA_{1c} assays has greatly aided the management of diabetes with accurate and comparable results [16]. Accordingly, we chose B-HbA_{1c} as the reference method for identifying diabetic and non-diabetic individuals. It may be argued that characterizing the participant as diabetic or non-diabetic based on B-HbA_{1c} instead of a clinical diagnosis may be inadequate and an oversimplification. However, it is a reproducible and consistent procedure that can be fit for a comparison with other diagnostic criteria. One has to keep in mind that glucose concentration is a snapshot of the metabolic status, whereas B-HbA_{1c} reflects the glycemic status during the life time of the erythrocytes. Both measurands have been recommended as decision criteria by the WHO.

Hemoglobin variants and factors that have an impact on the longevity of the erythrocytes can affect B-HbA_{1c} results. This potential source of ambiguity was minimized in the present study since the samples were analyzed using HPLC.

Reference intervals are based on measuring samples from a reference population [17]. The upper and lower limits of a reference interval are therefore liable to an uncertainty which includes the characteristics of the choice of reference sample population, the measurement uncertainty, the distribution of the results, and any transformation of data or other statistical procedures employed [18]. Decision limits, on the other hand, are concentrations that have been agreed by professional or regulatory organizations and bodies, often based on experience and biological variation of the measurand. Therefore, these limits should be understood as absolute and without an uncertainty. The use of globally recommended decision concentrations is a

Table 1 Contingency table of S-Glucose and P-Glucose versus B-HbA1c

S-Glucose (cutoff=6.9 mmol/L)							
B-HbA1c (cutoff=6.5%)		Negative	Positive	Total			95% CI
	Diabetic	9	138	147	Sensitivity	94%	0.89–0.97
	Non-diabetic	152	2	154	Specificity	98%	0.95–0.99
	Total	161	140	301			
		NPV=94%	PPV=99%		AUC	0.992	
P-Glucose (cutoff= 6.9 mmol/L)							
B-HbA1c (cutoff=6.5%)		Negative	Positive	Total			95% CI
	Diabetic	5	142	147	Sensitivity	97%	0.92–0.99
	Non-diabetic	147	7	154	Specificity	95%	0.91–0.98
	Total	152	154	301			
		NPV=97%	PPV=95%		AUC	0.994	

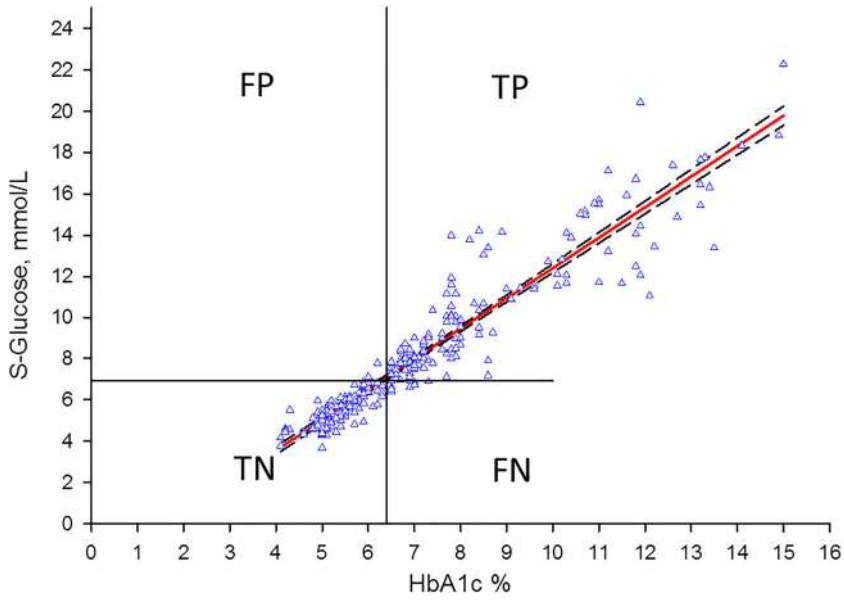

Fig. 5 Regression graph between S-Glucose and HbA_{1c}. Decision point is 6.9 mmol/L and 6.5% for S-Glucose and HBA_{1c}, respectively. Abbreviations: TP, true positive; TN, true negative; FP, false positive; FN, false negative

challenge for the laboratories to ensure that results are comparable and transferable and presently demonstrated by proficiency testing or external quality assessment schemes. Recently, a new ISO standard 21151 has been issued to offer a procedure to harmonize results of measurements by recalibration [19].

As expected, the mean and median of the S-Glucose concentration were lower than those of P-Glucose. The slope of the regression function is thus less than 1; hence, the difference between the results will increase with the concentration. The mean difference between the results was 0.3 mmol/L (5.6 mg/dL) in the diabetic group and 0.16 mmol/L (2.8 g/dL) in the non-diabetic group. The diagnostically important interval is close to 6.9 mmol/L (125 mg/dL) and the mean difference for the observations between 6.1 mmol/L (110 mg/dL) and 7.8 mmol/L (140 mg/dL) was 0.19±0.13 mmol/L (3.4±2.3 mg/dL) (2.8%). This is less than the ± 0.3 mmol/L (6 mg/dL) which is the standard acceptable analytical variation defined by the United States Clinical Laboratory Improvement Amendments guideline and thus not judged to be of clinical significance. The recent update of the European Federation of Clinical Chemistry and Laboratory Medicine list of biological variation indicates a within-individual variation of ± 0.3 mmol/L (6 mg/dL) [20]. Other studies report a higher P-Glucose than S-Glucose. For example, Kang et al. reported the mean glucose concentrations in plasma and serum to 6.61±0.55 mmol/L (119.4±9.9 mg/dL) and 6.02±3.6 mmol/L (108.5±6.5 mg/dL), respectively, among 1,254 participants [21]. The measurement procedure can also influence the recorded blood glucose concentrations and be liable to an analytical bias. A comparison of results from approximately 6,000 clinical laboratories revealed that the mean glucose concentrations measured in serum and plasma samples by a hexokinase method were essentially the same but when compared with a reference measurement procedure, a significant bias ($p < 0.001$) was observed in 40.6% of the peer groups [22].

We plotted the Sn, Sp, and LR(+) against the glucose concentration in a CDA graph [11] as a complement to a ROC curve, to single out the glucose concentration that optimally corresponds to the WHO global recommendation based on HbA_{1c}. In doing so, the Bayesian factor, i.e., the positive likelihood ratio (LR(+)), indicates the optimal choice of the cutoff if the objective was to identify the diseased with a balanced ability to also identify the non-diseased. However, LR(+), by definition, favors specificity, which may not be desirable in all clinical settings. If sensitivity and specificity are of equal clinical importance, the Youden index [23] is preferred as guidance and the local laboratory and clinic should make final adjustments of the cutoff; decreasing the cutoff will increase the sensitivity and decrease the specificity.

Many laboratories use serum-gel tubes for the majority of biochemistry and immunology tests. These tubes usually also provide a clotting accelerator. The introduction of S-Glucose for DM diagnosis and monitoring would reduce the need for special tubes for the measurement of P-Glucose and the amount of blood drawn from the patients. A simplification—lean performance—undoubtedly improves the laboratory workflow and thus the turn-around-time. The effects may be hard to quantify in general terms but in the laboratories of the authors we have recorded between 200 and 250 glucose measurements per day. This indicates a fair potential of reducing costs and also streamlining the logistics of tubes. Acceptance of S-Glucose in the diagnosis and management of the metabolic syndrome might facilitate the introduction, demand, understanding, and availability of a potentially powerful package of a short-term and a medium-long-term biomarker, S-Glucose, and serum fructosamine respectively, in the same sample. Further prospective studies in large sample size are needed for the improvement in guidelines.

Conclusion

Under the defined conditions, the diagnostic performance of S-Glucose and P-Glucose is comparable. The statistically significant difference between the results does not necessarily indicate a clinical significance, all other uncertainties considered. There is a strong correlation between B-HbA_{1c} and S-Glucose concentrations that validates the value of this measurand in practical clinical work. Diabetes mellitus can be accurately diagnosed with the same confidence in serum and plasma. An additional advantage of serum is using the same sample that may have been collected for a more extensive biochemical diagnosis. Applying this strategy would simplify logistics of preanalytical equipment, reduce the costs for special tubes, and simplify sampling.

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Author Contribution VP conceived the study design, performed the statistical analysis, and wrote the manuscript. AK repeated and validated the statistical analysis and approved the final version.

Declarations

Ethics approval The ethics committee of Nepal Health Research Council approved this study (protocol number 220/2021 P)

Informed consent Written informed consent was taken from each participant of this study.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Effects of dapagliflozin combined with short-term intensive insulin therapy on β-cell function in patients with newly diagnosed type 2 diabetes mellitus—a randomized controlled study

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Abstract

Purpose This study was aimed to evaluate the effect of dapagliflozin as add-on medication to short-term intensive insulin therapy on β-cell function in newly diagnosed type 2 diabetes mellitus (T2DM) patients.

Methods Sixty participants were recruited and randomized to receive either multiple daily insulin injections alone (MDI group), receiving pre-meal insulin aspart and insulin glargine at bedtime, or in combination with dapagliflozin 10 mg per day (MDI+DAPA group). Data was collected at baseline (d0), 14 days after reaching euglycemia (D14), and at the 12-week visit (W12). Fasting C-peptide concentration, areas under the curve (AUC) for C-peptide (CP) and insulin (INS), homeostasis model assessment (HOMA) indices, early insulin secretion index (EISI), and glycemic control were compared before and after treatment.

Results The two groups achieved euglycemia in similar time. Daily average insulin dosage in the MDI+DAPA group (0.27 ± 0.12 U/kg·day, $n = 28$) was lower than that in the MDI group (0.36 ± 0.22 U/kg·day, $n = 29$) ($p = 0.050$). HbA1c and plasma glucose were significantly decreased after treatment but of no significant difference between the two groups. Proportions of patients who achieved HbA1c ≤ 6.5% were similar (58.6% in the MDI group vs. 53.6% in the MDI+DAPA group, $p = 0.701$). Fasting C-peptide elevated after treatment but were comparable in the two groups. Both groups obtained similar improvements of AUC-CP, AUC-INS, HOMA-β, EISI, and HOMA-IR.

Conclusion Dapagliflozin as add-on could reduce daily insulin dosage, but bring no additive effect in improving β-cell function for newly diagnosed T2DM patients receiving intensive insulin therapy.

Trial registration The study was approved by the Chinese Clinical Trial Registry (ChiCTR.org.cn: ChiCTR1800015822).

Keywords Dapagliflozin · Intensive insulin therapy · β-cell function · Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, fundamental pathophysiological mechanism of which is deterioration of β-cell function and insulin resistance [1]. Researches manifested that at least 50% of β-cell function has been impaired when T2DM was diagnosed and the defect would progress over time [2–5].

Intensive insulin therapy has been proven to induce euglycemia without medication for over 1 year in some of the newly diagnosed T2DM patients [6–8]. The underlying mechanism might be elimination or alleviation of glucotoxicity and lipotoxicity [9].

Dapagliflozin, a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT-2), has shown favorable effects on both glycemic control and reduction of renal and cardiovascular outcomes [10, 11]. There were also reports on β-cell function improvement and insulin resistance reduction of dapagliflozin [12, 13].

Short-term intensive insulin therapy is recommended for newly diagnosed T2DM patients in clinical practice guidelines in China [14]. And in most medical centers, such patients were admitted in hospital to receive the treatment. Therefore, maximizing the efficacy of treatment during hospitalization is always crucial for endocrinologists. We wondered whether

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dapagliflozin as add-on medication could have extra effect on β-cell function and insulin resistance for newly diagnosed T2DM patients receiving intensive insulin therapy. Hence, the present trial, a randomized controlled study, was conducted.

Materials and methods

Study subjects

The trial started in March 2018 and the last patient was enrolled in August 2020. A total of 60 newly diagnosed T2DM patients, men and women aged between 18 and 75, without any usage of antidiabetic medication before, were enrolled. T2DM was diagnosed on the basis of the 1999 World Health Organization diagnostic criteria. Patients were excluded if they had: (1) severe acute diabetic complications including diabetic ketoacidosis and hyperosmolar nonketotic coma, (2) serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels > 3 times the upper limit of normal (ULN), or severe hepatic insufficiency, (3) eGFR < 60 mL/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease (MDRD) equation, (4) positive autoimmune antibodies against islets, (5) a recent history of being treated with corticosteroid, immunosuppressing drugs, or cytotoxic drugs, (6) known Cushing's syndrome, thyrotoxicosis, acromegaly, or other diseases that could have effects on blood glucose level, (7) known currently unstable or serious oncologic, infectious, malnutritious diseases, (8) allergies to contents of medications applied in the trial, and (9) been assessed by the investigators as being unsuitable for the study for other reasons including but not limited to psychiatric or psychosocial conditions.

Study design

All patients were hospitalized in the Department of Endocrinology of Dongguan Tungwah Hospital. A computer-generated randomization assigned participants into two equally sized groups. During hospitalization, all participants received diabetic education, including diet control, exercise, and glucose monitoring. Patients in the multiple daily insulin injection (MDI) group received pre-meal insulin aspart (NovoRapid®, Novo Nordisk) and insulin glargine (Lantus®, Sanofi) at bedtime. In the MDI plus dapagliflozin (MDI+ DAPA) group, patients were treated with dapagliflozin 10 mg per day in addition to the aforementioned MDI regimen. Initial insulin dosage was 0.4–0.6 IU/kg·day and total daily dosage was divided into 60% of prandial (20% for each meal) and 40% of basal. Capillary blood glucose were monitored at least 7 times per day, according to which daily insulin doses were titrated. Euglycemia was defined as fasting blood glucose ≤ 7.0 mmol/L and 2-h postprandial blood glucose ≤ 10.0 mmol/L. Once euglycemia was achieved (D1), the above treatments were maintained for 14 days. On the final day of treatment, the last insulin dose was insulin aspart before dinner (no bedtime insulin glargine). After suspension of medications, all patients were followed up for 12 weeks and required to maintain only diet and physical exercise control but no antidiabetic agents during this 12-week period.

Baseline data of all participants such as gender, age, blood pressure, height, weight, waist circumference, HbA1c, and lipid profiles were collected. All patients underwent a 75g-OGTT and serum glucose, insulin, and C-peptide were measured at 0, 30, 60, 120, and 180 min. These data were measured before treatment (d0), 14 days after reaching euglycemia (D14), and at the 12-week follow-up (W12).

Daily insulin dosages and adverse events including hypoglycemia, urinary infection, and DKA were also recorded.

The study protocol and informed consent document were approved by the Institutional Review Board and Medical Ethics Committee of Dongguan Tungwah Hospital (IRB Number: 2017DHLL018). All recruited patients provided written informed consent for participation. This study was registered at ChiCTR.org.cn with registration number of ChiCTR1800015822.

Study endpoints

In this study, the primary objective was to evaluate whether dapagliflozin as add-on medication to intensive insulin therapy could have extra effect on fasting C-peptide changes, in turn reflecting insulin secretory function. The primary endpoint was the fasting plasma C-peptide concentration, at D14 and W12. Secondary endpoint was areas under curve (AUC) for C-peptide. Other indices including AUC for insulin, homeostasis model assessment of insulin resistance (HOMA-IR), HOMA-β, and early insulin secretion index (EISI) were analyzed as exploratory endpoints.

Calculations

The above indices were calculated as follows:

(1) AUC for C-peptide and insulin were calculated using trapezoidal rule, e.g., $AUC\text{-}CP$ (ng/mL × h) = $(CP_{0\text{min}} + CP_{30\text{min}}) \times 0.5 / 2 + (CP_{30\text{min}} + CP_{60\text{min}}) \times 0.5 / 2 + (CP_{60\text{min}} + CP_{120\text{min}}) \times 1 / 2 + (CP_{120\text{min}} + CP_{180\text{min}}) \times 1 / 2$

(2) $HOMA\text{-}IR = FPG$ (mmol/L) × *fasting insulin (FINS)* (μIU/mL) / 22.5;

(3) $HOMA\text{-}\beta = 20 \times FINS$ (μIU/mL) / [FPG (mmol/L) − 3.5];

(4) $EISI = \Delta I30 / \Delta G30 = [INS_{30\text{min}}$ (μIU/mL) − $FINS$ (μIU/mL)] / [$GLU_{30\text{min}}$ (mmol/L) − FPG (mmol/L)].

Statistical analysis

Sample size calculation was based on the data of Fang et al. [15], which reported the fasting C-peptide at 12 weeks of T2DM patients receiving intensive insulin therapy with or without dapagliflozin. Based on their work, the difference of fasting C-peptide between the two groups is 0.2 ng/L (SD = 0.2 ng/L). Thus, the sample size required for analysis of the primary endpoint was 54 subjects, to ensure a two-sided significance level of 0.05 and statistical power of 0.90 with a drop-out rate of 15%.

Data were analyzed with IBM® SPSS® Statistics Version 22. Normally distributed data were presented as mean ± SD, and non-normally distributed variables (triglyceride, AUC-CP, AUC-INS, EISI, HOMA-IR, and HOMA-β) were expressed as median (interquartile range). Independent-sample *t*-test or Mann-Whitney *U* test was used to compare differences between two groups of normally or non-normally distributed data, respectively. Paired *t*-test or Wilcoxon signed rank test was performed to estimate the changes between each time point within the group. The χ^2 test or Fisher's exact test was applied to analyze the differences of proportions. A two-sided value of $p < 0.05$ was defined statistically significant.

Results

Baseline characteristics

The enrolled patients were 40.6 ± 8.6 years in age, and HbA1c of 11.8 ± 2.1% (Table 1). They were randomly assigned to the MDI group ($n = 30$) or the MDI+DAPA group ($n = 30$). One patient in the MDI+DAPA group did not finish therapy during hospitalization due to withdrawal of consent. At the subsequent 12 weeks visit, 2 patients (1 in the MDI group, 1 in the MDI+DAPA group) were lost to follow-up. Table 1 illustrates the baseline clinical characteristics of patients in the two groups. Most of them were comparable, except for family history and triglyceride. The positive rate of family history was significantly higher in the MDI+DAPA group (43.3%) than that in the MDI group (13.3%) ($p = 0.010$). Triglyceride also showed statistical difference, with 2.27(1.81) mmol/L in the MDI+DAPA group and 1.69(1.36) mmol/L in the MDI group ($p = 0.015$). Other indices including plasma glucose, C-peptide and insulin profiles, and β-cell function markers had no significant differences between the two groups.

Table 1 Baseline characteristics of study population

	MDI group ($n = 30$)	MDI+DAPA group ($n = 30$)	*p* value
Gender (male/female)	24(80.0) / 6(20.0)	24(80.0) / 6(20.0)	1.000
Age (years)	39.3 ± 7.9	41.9 ± 9.1	0.231
Family history (with/without)	4(13.3) / 26(86.7)	13(43.3) / 17(56.7)	0.010
Systolic pressure (mmHg)	121 ± 16	120 ± 17	0.841
Diastolic pressure (mmHg)	84 ± 13	80 ± 13	0.191
Weight (kg)	67.3 ± 10.0	71.0 ± 10.1	0.162
Body mass index (kg/m^2)	24.19 ± 3.47	24.83 ± 2.61	0.423
Waist circumference (cm)	88.6 ± 10.1	90.9 ± 6.5	0.302
HbA1c (%)	11.9 ± 2.2	11.6 ± 2.0	0.637
Fasting plasma glucose (mmol/L)	13.25 ± 3.69	14.92 ± 4.53	0.124
Fasting plasma insulin (mU/L)	9.00 ± 5.58	12.65 ± 14.89	0.213
Fasting plasma C-peptide (ng/mL)	1.74 ± 1.08	1.95 ± 1.05	0.456
Total cholesterol (mmol/L)	5.27 ± 1.02	5.30 ± 1.38	0.927
Triglyceride (mmol/L)	1.69(1.36)	2.27(1.81)	0.015
HDL-cholesterol (mmol/L)	0.98 ± 0.22	0.98 ± 0.25	0.960
LDL-cholesterol (mmol/L)	3.68 ± 0.98	3.30 ± 0.96	0.139
HOMA-β	22.34(23.60)	16.44(21.04)	0.701
EISI	0.316(0.86)	0.305(1.75)	0.595
AUC-INS (μIU/mL × h)	46.95(54.14)	42.34(55.31)	0.988
AUC-CP (ng/mL × h)	9.11(7.75)	8.71(8.30)	0.802
HOMA-IR	4.53(4.84)	5.03(5.82)	0.344

Data are presented as mean ± SD, median (interquartile range), or number (percentage) according to the type of data as appropriate. *HOMA* homeostatic model assessment, *EISI* early insulin secretion index, *AUC* area under the curve, *CP* C-peptide

Glycemic control and insulin dosage

All patients achieved euglycemia in the first week of therapy. The median time to reach euglycemia was 4.0(3.0) days in the MDI group, while the number was 3.5(2.0) in the MDI+DAPA group. There was no significant difference (p = 0.763). After achieving euglycemia, daily insulin dosages decreased gradually. There were no significant differences in average capillary FBG and 2hBG after achieving euglycemia between the two groups (Fig. 1). However, daily average insulin dosage in the MDI+DAPA group was lower than that in the MDI group (0.27 ± 0.12 versus 0.36 ± 0.22 U/kg·day, p = 0.050) (Fig. 1). After treatment, both at D14 and W12, HbA1c, FPG, and plasma glucose after a 75g-OGTT were all significantly decreased, but no difference was observed between the two groups (Figs. 2 and 3). Proportions of patients who achieved HbA1c ≤ 6.5% at W12 were similar in both groups (58.6% in the MDI group versus 53.6% in the MDI+DAPA group, p = 0.701).

Beta cell function and insulin resistance

Figure 3 illustrates the OGTT plasma glucose, C-peptide, and insulin profiles. They were generally comparable between the two groups at d0, D14, and W12, respectively. There was no significant difference of fasting C-peptide concentrations between the two groups, either at D14 or W12. In both groups, AUC-CP, AUC-INS, EISI, and HOMA-β were ameliorated significantly after treatment compared with baseline (Fig. 4). AUC-CP improved more significantly in the MDI+DAPA group than in the MDI group, at both D14 and W12. For EISI in the MDI+DAPA group, the improvement also sustained at 12-week visit (p = 0.004, D14 vs. W12), while no similar amelioration could be found in the MDI group. In addition, AUC-INS increased after treatment, but the improvements in the two groups were similar. However, there was no such improvement in HOMA-β at W12 compared with that at D14. HOMA-IR reduced significantly after treatment at D14 compared with baseline in both groups. At the 12-week visit, HOMA-IR in both groups elevated, but only in the MDI group showed significant difference compared with D14 (p = 0.035).

Adverse events

During the hospitalization, the incidence of hypoglycemia which was defined as capillary blood glucose level < 3.9 mmol/L was similar in both groups (29 times in the MDI group, 28 times in the MDI+DAPA group, p = 0.666). There were 3 cases of urinary infection in the MDI group, while 1 was observed in the MDI+DAPA group. Rate of incidence showed no significant differences (p = 0.611). Not any case of DKA was observed.

Discussion

The current study assessed the effect of dapagliflozin as add-on agent to MDI treatment on β-cell function and insulin resistance in newly diagnosed T2DM patients. By using a 75g-OGTT, we found that dapagliflozin combined with short-term intensive insulin therapy did not bring extra benefit in amelioration of pancreatic β-cell function.

Progressive β-cell dysfunction is the basic mechanism of the development or deterioration of hyperglycemia [1]. For newly diagnosed type 2 diabetic patients, preserving their β-cell function to the largest extent is essential. Intensive insulin therapy, by fast correction of glucotoxicity and lipotoxicity, is able to induce durable amelioration in insulin sensitivity, leading to long-term glycemic remission [6–8]. Thus, short-term

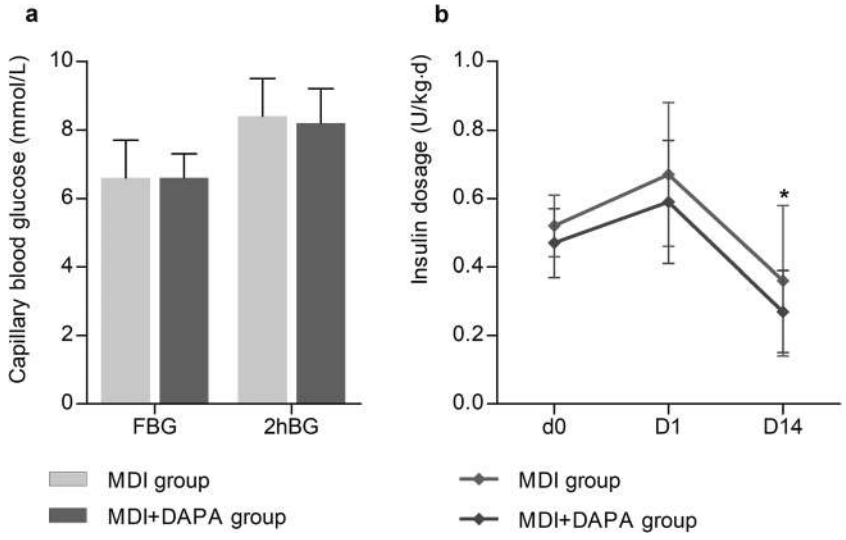

Fig. 1 **a** Mean capillary blood glucose after reaching euglycemia and **b** daily insulin dosage of the two treatment groups. *p < 0.05 for comparison between the two treatment groups. FBG, fasting capillary blood glucose; 2hBG, 2-h postprandial capillary blood glucose; d0, baseline; D1, the day when achieved euglycemia; D14, the 14th day after achieving euglycemia

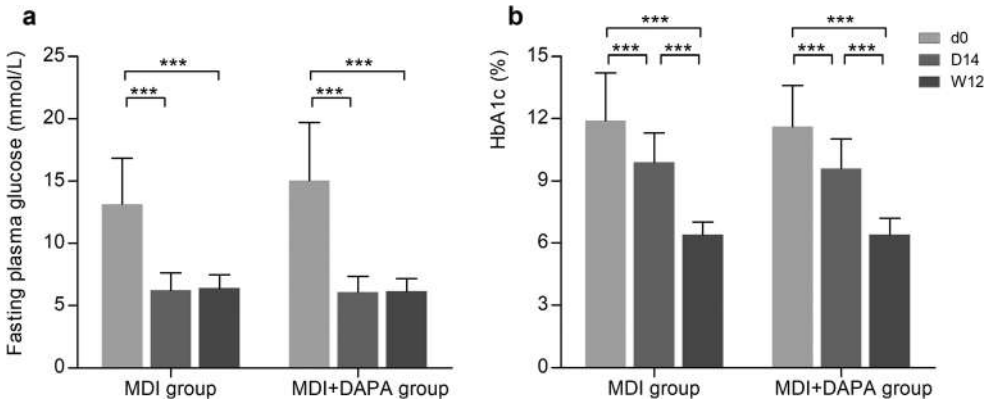

Fig. 2 Glycemic control of the two groups, **a** fasting plasma glucose, and **b** HbA1c. ***$p < 0.001$. d0, baseline; D14, the 14th day after achieving euglycemia; W12, the 12-week visit

intensive insulin therapy is recommended for newly diagnosed T2DM patients in clinical practice guidelines in China [14]. Recent clinical researches revealed that dapagliflozin, or other SGLT-2 inhibitors, improved β-cell function and insulin resistance, which might be due to mitigation of glucotoxicity [12, 13, 16, 17]. Ferrannini et al. [18] even reported an immediate improvement after just one single-dose of empagliflozin.

To our knowledge, no previous study has evaluated β-cell function of dapagliflozin as add-on to short-term intensive insulin therapy for newly diagnosed T2DM patients. In the current study, OGTT-derived C-peptide and insulin profiles after treatment at D14 and W12 were significantly increased in both groups. All the other β-cell function indices also improved, thereby confirming the efficacy of the intervention in this

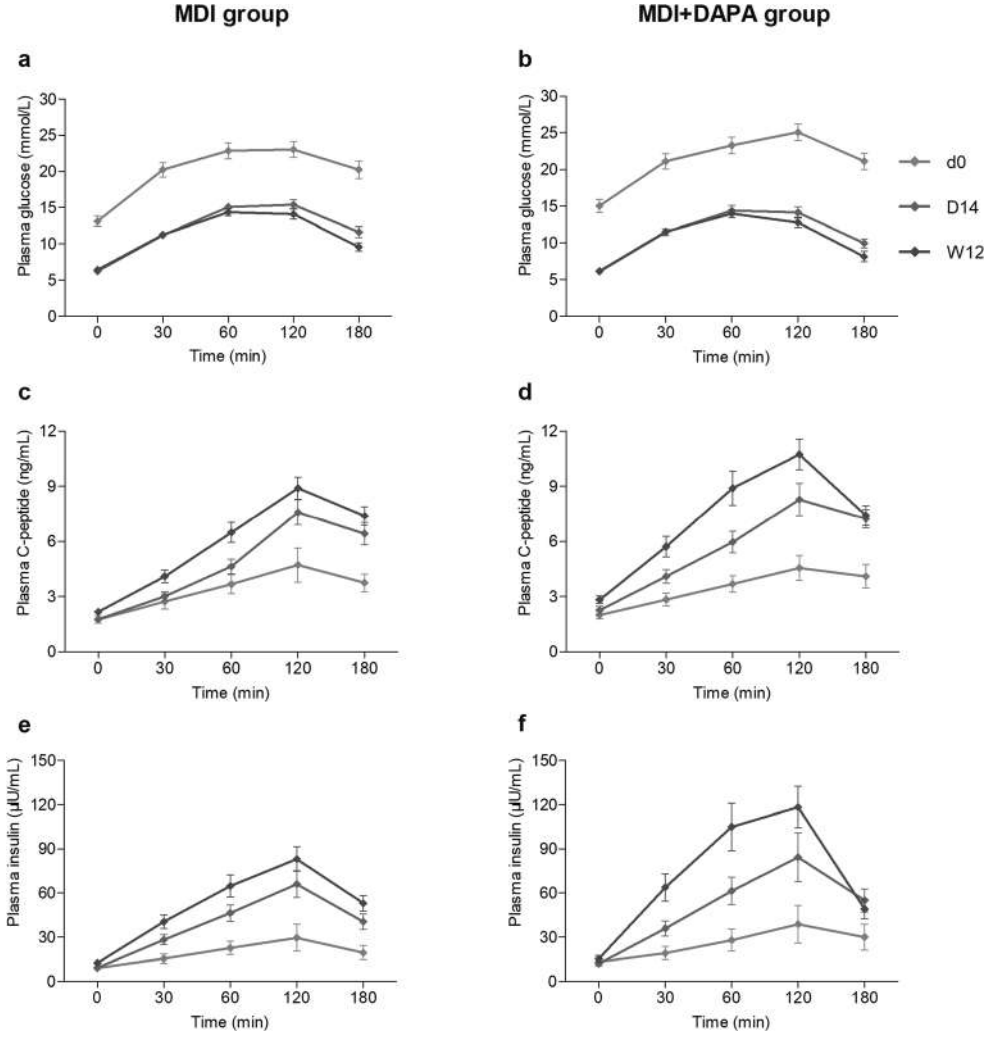

Fig. 3 Plasma (**a**, **b**) glucose, (**c**, **d**) C-peptide, and (**e**, **f**) insulin concentrations after a 75g-OGTT of the two groups. Plots represent mean ± SEM. d0, baseline; D14, the 14th day after achieving euglycemia; W12, the 12-week visit

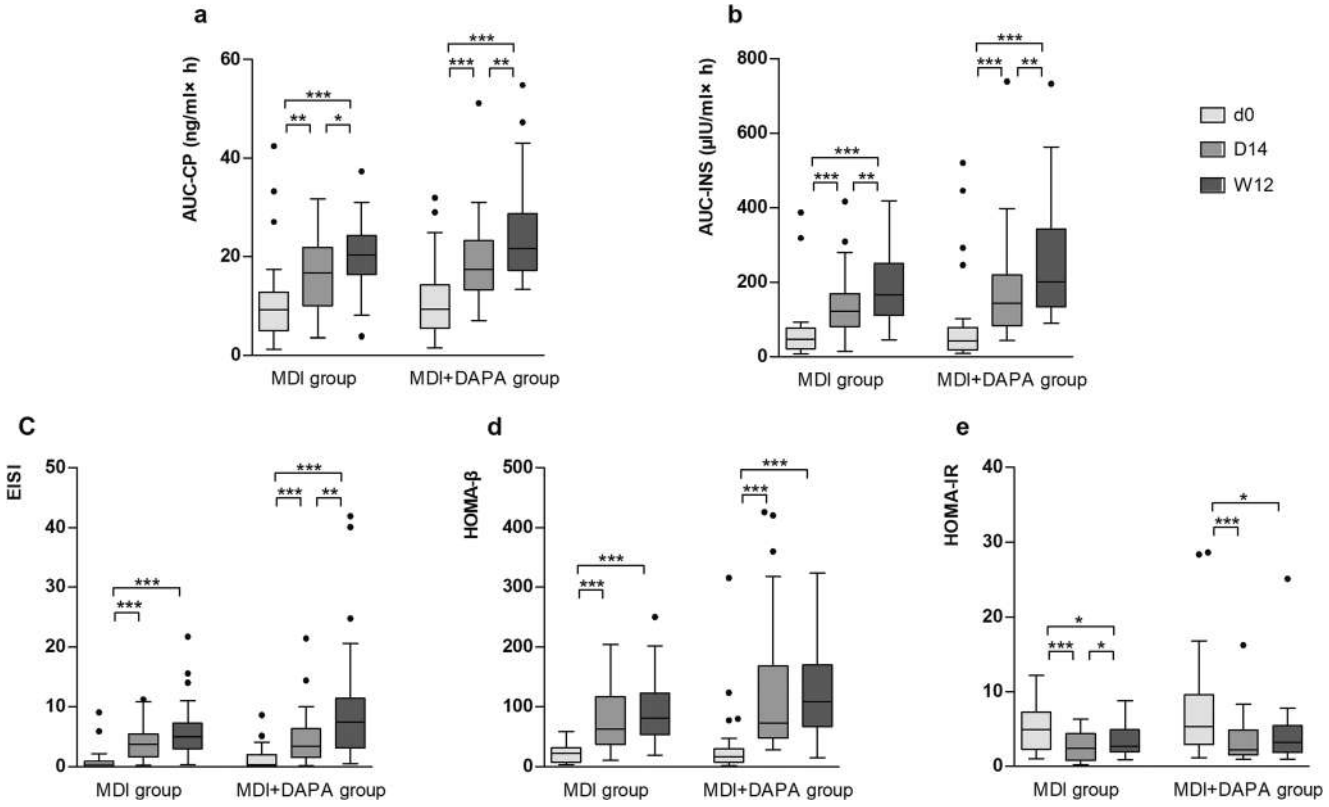

Fig. 4 Box plots of β-cell function indices, **a** AUC-CP, **b** AUC-INS, **c** EISI, **d** HOMA-β, and **e** HOMA-IR. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. AUC-CP, area under the curve for plasma C-peptide; AUC-INS, area under the curve for plasma insulin; EISI, early insulin secretion index; HOMA, homeostasis model assessment; d0, baseline; D14, the 14th day after achieving euglycemia; W12, the 12-week visit

patient population. However, there were no significant differences between the two treatment groups, indicating that dapagliflozin does not further enhance the effect of short-term intensive insulin therapy on β-cell function. As mentioned above, there were researches revealing that SGLT-2 inhibitors could improve β-cell function [12, 13, 16, 17], but they were applied as mono-therapy and compared with other antidiabetic agents or placebo in those studies. Their improvements were closely correlated with decrement of plasma glucose, implying that β-cell function amelioration was mainly resulted from elimination of glucotoxicity. In our study, all patients in both groups achieved euglycemia in 1 week and maintained similar glycemic control even after cessation of treatment. Thus, it was not surprising that their improvements of β-cell function indices were similar.

However, when comparing with themselves at different time points, we found that AUC-CP improvement was more significant in the MDI+DAPA group. Remarkably, after suspension of treatment, dapagliflozin provided a sustained significant improvement of EISI at D14 while no such change was observed in the MDI group. As EISI takes into account the 30-min response upon glucose stimulation, it is more sensitive for evaluation of the early phase of insulin release than other indices used in the study. It is also reported that SGLT-2 inhibitors mitigate insulin resistance [12]. In the current study, we observed a decrease of HOMA-IR after treatment, but elevation after suspension of medication. Interestingly, with the use of dapagliflozin, the elevation was not significant. Taken together, we suggest that the prolonged improvement of EISI is most likely due to amelioration of insulin resistance. But as these were explorative indices, further researches designated EISI as primary endpoints were needed to confirm our findings.

The present study also demonstrated a significant reduction in plasma glucose levels after treatment at D14 and even after cessation of medication at W12. This acknowledged the role of dapagliflozin plus MDI therapy in glycemic control for newly diagnosed T2DM patients. Furthermore, dapagliflozin reduces daily insulin requirement as expected, reaching the same level of blood glucose with those accepting MDI alone. However, there was no difference of HbA1c, fasting plasma glucose, or number of patients who achieved euglycemia after treatment suspension between the two groups, indicating the short-term use of dapagliflozin does not bring additive effects on glycemic control for patients receiving MDI therapy.

As SGLT-2 inhibitors lower plasma glucose by enhancing urinary glucose excretion, urinary infections are known adverse effects. However, the current study did not observe a difference between the two treatment groups. Plus, due to its insulin-independent antidiabetic mechanism, dapagliflozin did not cause apparent increase in hypoglycemia. Therefore, dapagliflozin is sufficiently safe.

There were some limitations in this study. First, the primary endpoint of the study, fasting C-peptide concentration, was one of the easiest but apparently not the best index to measure pancreatic β-cell function. Hyperglycemic clamp is by far the gold standard to evaluate β-cell function, but it is costly, time-consuming, and difficult to implement. Researches revealed that chronic hyperglycemia may deteriorate meal- and glucose-induced endogenous insulin secretion, somewhat confounding C-peptide and insulin response [19, 20]. On the contrary, fasting serum C-peptide is not associated with baseline glycemic control [20, 21] and is simple for assessment of basal endogenous insulin secretion in daily clinical practice. As participants recruited in this study were drug-naive, glucotoxicity probably existed. In this case, the lack of influence of baseline HbA1c on fasting C-peptide might be helpful to evaluate the residual beta-cell function. Second, the sample size estimation was based on the primary endpoint, so when analyzing the other indices, it might be relatively small and reduce the statistical power. Future studies with a large enough sample size setting other indices such as EISI as primary endpoint will be needed to further explore the question. Third, the study population might not be a good representative for general T2DM patients. Dapagliflozin was approved for only 1 year in China when the study began. Most patients were reluctant to participate in a study on a somewhat new drug.

In conclusion, dapagliflozin as add-on medication was effective and safe in glycemic control and could reduce daily insulin requirement, but it did not bring additive effects on improvement of β-cell function for newly diagnosed T2DM patients receiving short-term intensive insulin therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-022-01089-w.

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Availability of data and material Data sharing will be considered only on a collaborative basis with the principal investigators, after evaluation of the proposed study protocol and statistical analysis plan.
Code availability Not applicable.

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Declarations

Ethics approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol and informed consent document were approved by the Institutional Review Board and Medical Ethics Committee of Dongguan Tungwah Hospital (IRB Number: 2017DHLL018) and the Chinese Clinical Trial Registry (ChiCTR.org.cn: ChiCTR1800015822).

Consent to participate All recruited patients provided written informed consent for participation.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

National and regional prevalence rates of diabetes in Saudi Arabia: analysis of national survey data

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Abstract

Background The prevalence of diabetes mellitus (DM) has grown globally including Saudi Arabia. However, there are no recent national and regional reports about DM in Saudi Arabia. Therefore, this study aimed to explore the national and regional prevalence rates of DM among the Saudi population.

Methods Data from an ongoing household health survey that was carried out by the General Authority for Statistics in 2017 was utilized in this study. The study sample was selected by including 24,012 households which was representative of the population and distributed according to the 13 administrative regions. A self-reported diagnosis of DM was collected by asking subjects if they have been diagnosed by a doctor.

Results The proportion of DM was 8.5% among the Saudi Arabia population (≥ 15 years) and was higher in male (10.3%) than female (9.9%). The prevalence of DM among the age group ≥ 60 years was the highest (49.2%), followed by the age group 45–64 years (38.9%) while the lowest prevalence was found among the younger group < 40 years (15.3%). There was a large difference between regions ranging from 7.3% in Najran to 11% in Makkah.

Conclusion This study showed the recent national and regional prevalence rates of DM among Saudi populations. The high prevalence of DM in Saudi Arabia requires an urgent public health call to improve early detection program and lifestyle interventions. This study urges to minimize the health and economic burden of DM by establishing and implementing a national diabetes prevention program.

Keywords Diabetes · Elevated blood glucose · Saudi Arabia · Prevalence · Epidemiology

Introduction

Diabetes mellitus (DM) is an ever-increasing worldwide health concern. Over the past decades, the prevalence of DM has significantly increased worldwide and currently reaching an epidemic proportion [1]. The most up-to-date stats according to the International Diabetes Federation (IDF) indicated that 9.1% among adults whose age ranges from 20 to 79 years, or 463 million people, have DM. Moreover, 374 million people live with impaired glucose tolerance and are especially at risk of DM later in their life. So far, about half (232 million people) of the adults with DM remain undiagnosed, many potentially developing complications while unknowing their problem [2, 3].

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Complications associated with the inadequate treatment of DM are very debilitating and life-threatening. Compared to people without DM, adults with DM are likely to develop macrovascular disorders (including coronary, cerebral, and peripheral vascular disorders), which are considered the major causes of death in people with DM and microvascular disorders (such as diabetic neuropathy, retinopathy, and nephropathy) [4]. DM therefore imposes a huge health and financial burden on people, healthcare systems, and countries. Global estimates indicated that 10% (USD 760 billion) of the total health expenditure in 2019 was spent on DM [2].

A number of reports have indicated that prevalence of DM is expected to be high in the Middle East region and North Africa, which probably attributed to the increased per capita income, economic progress, urbanization, and pronounced lifestyle changes that enabled physical inactivity and raised the rate of obesity [2, 5, 6]. Saudi Arabia is not so far from this global epidemic [7, 8]. Several surveys have documented that the prevalence of DM among Saudi population reached a disturbing proportion [9]. As reported by Saudi Arabia Ministry of Health, the prevalence of DM has considerably increased from 0.9 million people in 1992 to 2.5 million people in 2010, showing almost 3-fold increase in the prevalence rate in less than two decades [8, 10]. According to the World Health Organization (WHO) report, the Kingdom of Saudi Arabia is on the highest end of the spectrum regarding the prevalence of DM in the Middle East, recording 21.8% of all Saudi population in 2008 with DM [11]. A community-based epidemiological study reported that the prevalence of DM was 23.7% in people aged 30 to 70 years [3]. A cross-sectional study conducted in 2009 that collected data from a sample of 6024 Saudi subjects (age, 55.3 ± 13.2) indicated that the overall prevalence is 30% among Saudi population on DM and past medical history [12]. However, these studies have a number of limitations such as small and under-representative sample size, and lack of age-specific prevalence.

Despite international organizations such as IDF and WHO providing data about the prevalence rate of DM, by countries, these data may have some limitations in statistical precision because they are mostly calculated based on imputations [13]. Considering the growing-prevalence of DM over time, data from the above-mentioned studies may differ from the current rates of prevalence of DM. In addition, the samples recruited only from certain regions and may not give a true prevalence rate among Saudi Arabia.

A necessary first-step toward framing of etiological hypotheses, identifying the healthcare priorities, generating policy initiatives, and evaluating how effective are the healthcare services in mitigating the burden of DM is to establish national and regional registries. Therefore, to enhance our knowledge about the national prevalence of DM and compare it with other prevalence studies, this descriptive epidemiological study has been undertaken with the aim of estimating the national as well as the age-, gender-, and region-specific prevalence rates of DM among Saudi population.

Materials and methods

The design of this study was cross-sectional descriptive research. This study was part of a large Kingdom-wide screening using an ongoing household health survey that was carried out in 2017 by the General Authority for Statistics (GASTAT). The selected study sample was selected by including about 24,012 households that were recruited from 1334 enumeration areas as being representative of the survey community throughout the administrative regions in the Kingdom of Saudi Arabia [14]. Inclusion criteria included all individuals (Saudi and non-Saudi) residing in Saudi Arabia aged 15 years and older at the time of data collection as well as Saudi household members who were out of the country for education, trade, or tourism.

The method of selecting sample units from the statistical structures aimed at including the target population was carried out in two phases. The main sampling units were chosen in the first phase. These sample units were the enumerated regions that were part of the buildings and residential property enumeration and coding stage. From all administrative regions, 1334 enumeration areas were chosen by employing a proportional-size approach and weighting the overall Saudi Arabian sample of households. The following phase was to randomly collect the final sampling units from the statistical areas. By that time, the households in the enumeration areas (that were selected during the first phase) were selected by using the regular random sampling resulting in a total of 24,012 households throughout the Kingdom (Fig. 1). Each head of household or any adult member of the household, who is familiar with its affairs, was interviewed by a qualified field researcher from the GASTAT to record all data electronically on an iPad system.

After identifying the optimal size of the survey sample of homes in each administrative region, the primary sampling units were then drawn from the main sample population. The primary sample framework of the home surveys yielded a total of 1334 counting locations. The sampling process is illustrated in Fig. 1.

Data collection was carried out via trained research assistants. Those data collectors were selected based on educational level, field work experience, personal attitudes, successful completion of the training program, and age of above 20 years. Training program included practical and hands-on lectures on technical, administrative, and awareness materials that were utilized in data collection processes. This training program lasted for 1 week. Data collectors were also introduced to the objectives of the survey and detailed explanation

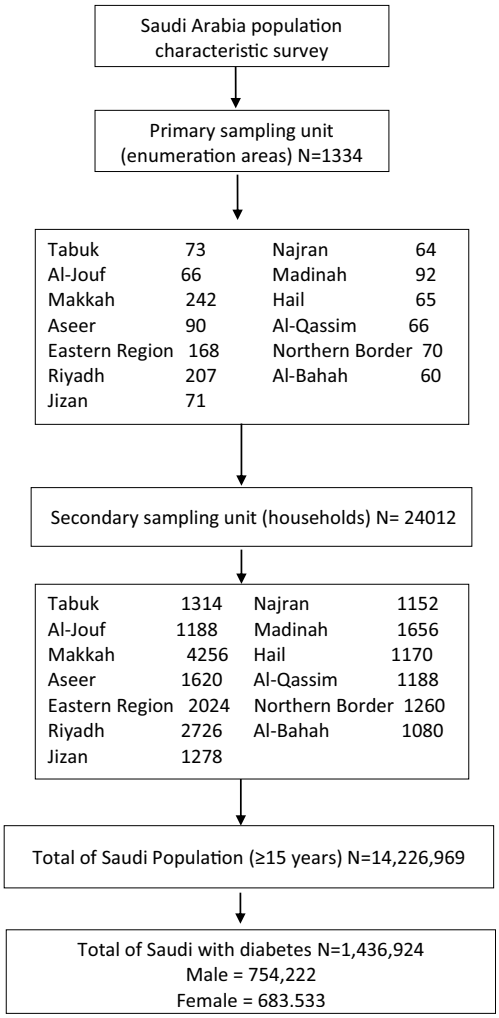

Fig. 1 The flowchart of the survey sample selection

of the questions and items in the questionnaire. Finally, data collectors were trained on how to deal with public and asking questions in record time to ensure efficiency of data collection.

In the current study, a self-reported diagnosis of diabetes was collected. The interviewed individuals were asked if any one of the household members have been diagnosed by a doctor and informed him/her that he/she has diabetes and were categorized as having DM in the study.

Statistical analysis

Data analyses were performed using statistical software Stata version 15.1 (Stata Corp, College Station, TX), and prevalence thematic mapping was generated via a web-based map customization tool (SimpleMaps.com, Pareto Software, LLC©, USA).

For the purpose of the current study, prevalence rates (%) of DM diagnosis (i.e., the basic descriptive epidemiology) were calculated for the entire sample. To generate insights into the age, gender, and geographic variability, the prevalence rates have also been calculated for the age-, gender-, and administrative region-stratified subsamples.

Results

The proportion of the population diagnosed with DM reached 8.5% among the population of Saudi Arabia 15 years and over, and the percentage rises between the male populations to reach (10.3%), while the female population was 9.9%. This percentage for the total Saudi population including all age groups was 10.1%. The prevalence among the age group (≥ 65 years) was the highest, recording 49.2%, followed by the age group 45–64 years that reached 38.9%, and the lowest prevalence was found among those who were younger than 40 years old as 15.3%.

Figure 2 illustrates the number of people aged 15 years and over, who are diagnosed with DM according to gender and age groups. The percentage of Saudis diagnosed with DM increases significantly with increasing age and that the rates of prevalence increase significantly at the age of 40 years and older compared to those who were under the age of 40 years; the prevalence of diagnosed DM in the Saudi population is the highest at the age of 65 years or more, where there is a large convergence in the ratio between males and females, as the ratio reached 48.9% for Saudi males while it reached 49.4% for Saudi females.

Figure 3 shows the national and prevalence rate of DM per 100,000 people among Saudi population. The highest prevalence of diagnosed DM was seen in the Makkah region (11%), followed by Hail with a rate of 10.8%, and the lowest percentage was recorded in the Najran region (7.3%).

Discussion

DM is one of the leading causes of death in Saudi Arabia [15]. This study suggests large differences in prevalence of DM based on age, gender, and Saudi regions. The highest prevalence rate of DM was in the older age category (i.e., > 65 years old), male gender, and in the Makkah region. The data present an increase of the prevalence of DM corresponding to aging for both genders.

These data suggest alarmingly high prevalence and change in the prevalence of DM has over the years. The rate of DM in Saudi Arabia was in the top 10 countries based on the International Diabetes Federation for people who aged between 20 and 79 years old [16]. There were dramatically increases in the prevalence of DM in Saudi Arabia, from 7% in 1989 to 32% in 2009 [17]. Based on the American Diabetes Association diagnostic criteria, a recent community-based

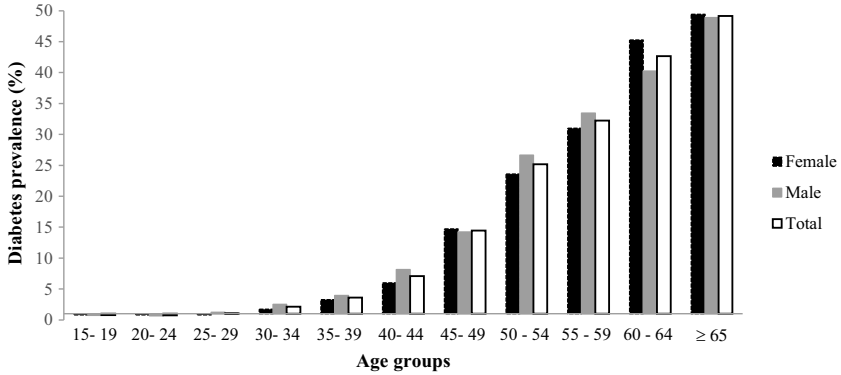

Fig. 2 Diabetes prevalence across gender and age groups

study showed 15.7% of Saudi population with DM which was in parallel with Turkish population and higher than Chinese population results [18]. The findings of this study suggest a lower prevalence compared to these results with large differences in prevalence between regions. However, these ranges were in parallel with the overall prevalence of DM in the USA [19]. Future studies may need to use high standard diagnostic criteria for DM to clarify the actual percentage of DM based on the types and risk factors in Saudi regions. This will help in identifying preventive strategies and treatment protocols for DM management centers around the Kingdom.

Risk factors for DM have been examined previously and include age, sex, and overweight or obesity. The prevalence of DM increased with age in the current study, and this was a common risk factor in Western countries such as the USA and China [20, 21]. In addition, previous evidence found similar results to our study regarding age (> 45 years) as a risk factor for DM in Saudi population [18, 22]. Aging has been linked with increased adiposity and lower muscle mass that might affect insulin sensitivity leading to DM [23, 24]. Males were found to have higher prevalence of DM when compared to males in the current study. These findings are consistent with previous evidence at a global level (9.0% in males, 7.9% in females) [25]. The difference in DM prevalence between men and women could be attributed to the predisposing risk factors in men such as being at risk for DM at a lower body mass index, and smoking [26]. Furthermore, previous research found similar trends for the higher prevalence of DM in men compared to women due to smoking, alcohol intake, and presence of other diseases such as hypertension and dyslipidemia [27, 28]. Overweight and obesity are the most common risk factors for DM globally and locally [17, 18, 22]. However, in

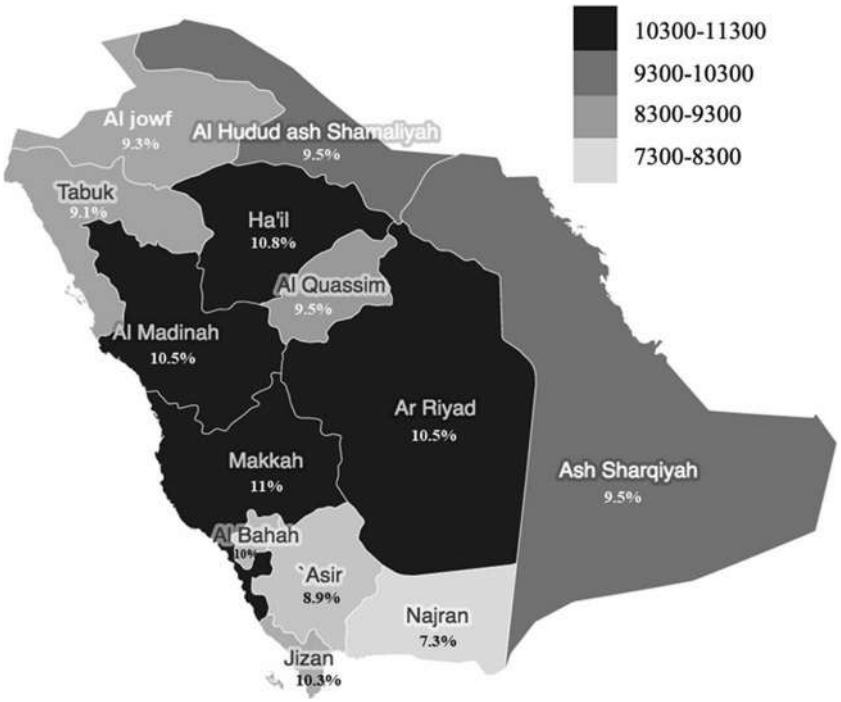

Fig. 3 The national and regional prevalence rates of diabetes per 100,000 people

the current study, overweight or obesity was not available. Future research should examine the associated risk factors with DM at a national level.

Lifestyle interventions have a significant impact on prevention of DM [29]. However, the data on Saudi lifestyle were not available. Our previous evidence has examined the prevalence of physical activity at a national level [30]. According to the findings of this study, the prevalence of satisfying physical activity recommendations (150 min/week) was 17.40% in Saudi population. This very low prevalence might be linked to the increased prevalence of DM. Although the Makkah region had the highest prevalence of practicing physical activity (23%) [30], it has the highest prevalence of DM (11%). These findings could be explained by the population living in this region. However, it is crucial to examine factors that affect DM distribution among regions in Saudi Arabia. Lifestyle modification has shown positive results on the prevention of DM or at least delay it. Physical activity and diet counseling are important interventional approaches for people who are at risk of DM. In addition, a cost-effective program such as lifestyle modification might help in establishing prevention programs for people living in the Kingdom of Saudi Arabia.

There are several limitations to this study that should be addressed in future research. The cross-sectional design of this study may lead to selection bias. There is a need to design multicenter longitudinal study from different regions and organizations. The diagnosis of DM was based on self-reported and highly standard diagnostic criteria using a gold standard–based screening study are imperative to be utilized in future studies. Another limitation is the lack of disease parameters such as duration and glucose level of glycemic control such as hemoglobin A1c. Future work should include such parameters for further understanding of the disease progression and impact in Saudi Arabia. Understanding other risk factors of DM will help in investigating the other associated risk factors with the DM diagnosis. This study did not distinguish type 1 and type of DM. Therefore, future research should examine the prevalence of each type at the national and regional level. Finally, we recommend including demographics such as education, ethnicity, occupation, marital status, and insurance coverage to help in optimizing the DM management for Saudi population.

Conclusion

This study showed the recent national and regional prevalence rates of DM among Saudi populations with large variations in prevalence by age, sex, and region. Future studies are needed to consider high-quality design and methods to help preventive strategies and DM management approaches in Saudi regions. Future studies are needed to investigate the effect of demographics including education, economy, ethnicity, and medical coverage on DM distribution based on different regions in the Kingdom of Saudi Arabia. In addition, there is a necessity to understand the prevalence of DM in corresponding with the risk factors related to DM such as obesity, smoking, and physical inactivity among Saudi population.

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Author contribution BA is involved in the study design. AA and BA helped with data analysis and interpretation. BA, AA, MMA RKA, and KK helped in writing and reviewing the final version of this manuscript.

Declarations

Conflict of interest KK has acted as a consultant and speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG/Menarini Group, Janssen, and Napp.

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ORIGINAL ARTICLE

Follow-up frequency impacts metabolic control in diabetes patients under MMC framework—a retrospective study

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Abstract

Background Patients with type 2 diabetes mellitus (T2DM) have risk of cardiovascular complications if blood glucose, blood lipids, and blood pressure (BP) are not optimally controlled. National Metabolic Management Center (MMC) has established a new management model to improve metabolic control.

Purpose This study aimed to assess the level of metabolic control in T2DM patients under MMC and explore the relationship between clinical follow-up frequency and target-reaching rate of HbA1c, LDL-C, and BP.

Method This was a retrospective study. Baseline measurements and follow-up data were collected from September 2017 to November 2019. The subjects were grouped according to the follow-up frequency as <4 times/year, =4 times/year, and >4 times/year.

Results The positive changes in HbA1c and LDL-C were associated with follow-up frequency. After adjusting for confounders, the target-reaching rate of HbA1c for patients with follow-up ≥4 times/year was higher than those with <4 times/year, with odds ratios of 1.518 (=4 times/year) and 1.508 (>4 times/year). Compared to patients with follow-up <4 times/year, the target-reaching rate of LDL-C for patients with follow-up ≥4 times/year was higher, with odds ratios of 1.998 (=4 times/year) and 2.517 (>4 times/year). After 1 year of management, 48.91%, 47.43%, and 56.72% of patients achieved the target goals, respectively. 12.88% patients met all three targets.

Conclusion MMC improves the target-reaching rate of HbA1c, BP, and LDL-C for T2DM patients in China. Compared with follow-up <4 times/year, follow-up 4 times/year has the maximum benefit of metabolic control in patients while >4 times/year was found no additional benefits than 4 times/year.

Keywords Follow-up frequency · Chronic disease management · Metabolic control

Jiaohong Luo and Xianqin Long contributed equally to this work.

Jiaohong Luo, Chenyun Xu, Ying Wang, and Min Li hold author country's registered Nurse license (RN).

Highlight
(1) MMC care improves the target-reaching rate of metabolic control for patients with type 2 diabetes
(2) Compared with <4 times/year follow-up frequency, 4 times/year follow-up has the maximum benefit of metabolic control in diabetic patients, while >4 times/year had no additional benefits

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Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide and is the leading cause of death and disability [1]. Patients with type 2 diabetes mellitus (T2DM) often need effective measures of management for optimum metabolic control. One of the important measures to facilitate patient self-management is the follow-up appointment [2]. A previous study showed that follow-up appointments with care providers significantly reduced patients' HbAlc levels [3]. However, a meta-analysis indicated absenteeism rates of 4–40% in patients with diabetes and non-attendance in follow-up appointments interrupting the continuity of care and effective disease management [4]. Hence, the lack of follow-up appointments of the patient with the diabetes care provider is a potential reason for failure to achieve long-term glycemic control.

The American Diabetes Association (ADA) guidelines recommend patient's visits to their healthcare provider every 3 to 6 months [5]. However, the frequency of annual follow-up visits in patients with T2DM to achieve the maximum benefits of metabolic control has not been reported. Due to the difference in the healthcare system in China, patients with chronic diseases like diabetes do not take follow-up appointments and visit hospitals or clinics only on feeling uncomfortable or for the refilling of their prescriptions, which largely contributes to poor metabolic control. A multi-center study survey in mainland China showed that only 5.4% of patients with T2DM met recommended targets for HbA1c, BP, and LDL-C in 2010 [6]. The low target-reaching rate suggested for active assistance to patients to achieve comprehensive control of blood glucose, blood pressure, and blood lipids. National Metabolic Management Center (MMC) was established in 2016 in China as a new metabolic management mode and aimed to achieve the best metabolic role in patients by providing comprehensive management and long-term support from the hospital both internally and externally. Under the core concept of "one center, one station, one standard," the screening, diagnosis, treatment, and follow-up of metabolic diseases such as diabetes and complications are standardized in hospitals of different levels in different regions of the country through the establishment of standardized diagnosis and treatment technology and management process. In these places, advanced diagnosis and treatment equipment and Internet of Things technology are integrated into an online and offline integrated overall solution, and MMC doctor-side and patient-side APP management software is used to interconnect hospital and external information of patients, so as to achieve all-round management of patients with metabolic diseases such as diabetes [7].

The objective of our study was to evaluate the level of metabolic control in T2DM patients under MMC and explore the relationship between follow-up frequency and the target-reaching rate of HbA1c, LDL-C, and blood pressure.

Methods

Study design and participants

This was a retrospective study where the participants were recruited from an independent digital medical record system which is established in the outpatient clinic of the Endocrinology and Metabolism Department of Second People's Hospital of Yuhuan, Zhejiang Province, China. The inclusion criteria in this study were diagnosis of T2DM based on the 1999 diagnostic criteria of the WHO; the patients had no disturbance of consciousness and voluntarily joined the MMC center. Patients who were pregnant, with psychiatric disorders, or with critical conditions were excluded. The study was conducted from September 2017 to November 2019 (2019LL017).

Data collection

Baseline data

The patient's information was obtained from an independent digital medical record system established by MMC. The MMC care includes the collection of medical history, including symptoms, medication history, lifestyle, and adverse events; laboratory tests, including glucose tolerance tests, routine and biochemical tests, and renal function tests; medication adjustment; and diabetes self-management education and support.

Laboratory testing

The metabolic profile was monitored including the fasting blood glucose (FPG), 2 h postprandial glucose (2 hPG), and glycosylated hemoglobin A1c (HbA1c), and the lipid profile including triglycerides (TGs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and systolic and diastolic blood pressure (BP). The blood glucose index was analyzed by Roche Cobas 600 automatic biochemical analyzer, and HbA1c was measured by American Beller D-10. The data sources for the study were obtained from data stored in electronic medical records.

The primary study outcomes included HbA1c, LDL-C, and BP reaching the target levels during the study period with HbA1c < 7.0%, LDL-C < 2.6 mmol/L, and blood pressure < 130/80 mmHg. These target goals were consistent with the

guidelines for the prevention and control of T2DM in China [7]. Blood glucose was detected by the hexokinase method (Architect C16000, ABBOTT), and the oxidase method was used for the detection of lipids (Architect C16000, ABBOTT). HbA1c levels were determined by high-performance liquid chromatography (HPLC) on Mindray H50.

Statistical analysis

Statistical analysis was calculated by SPSS 22.0. All values were described as mean and standard deviation (SD) or median (25–75th percentile) for continuous normal or non-normal variables and frequencies (%) for categorical variables. One-way ANOVA was used for data with a continuous and normal distribution, and the Wilcoxon rank-sum test was used for non-normal distributed data. Categorical variables were compared using the chi-square tests. Logistic regression was used to explore the factors that affect the target-reaching rate of HbA1c, LDL-C, and BP with adjustment of confounders, the odds ratios (ORs), and the corresponding 95% confidence intervals (CIs) were calculated. p values < 0.05 were considered statistically significant.

Result

A total of 3455 patients were enrolled in the study. The participants not fulfilling the inclusion criteria were excluded, and 3035 cases were finally included. The demographic and clinical characteristics of the 3035 eligible subjects are shown in Table 1. The mean age and diabetes duration were 56.08 years (*SD* = 10.58) and 7.08 years (*IQR*: 1.33 10.83). The mean HbA1c and LDL-C levels were 8.22% (*SD* = 2.10) and 2.87 mmol/L (*SD* = 0.97) at the baseline. About 25.1% of patients had dyslipidemia, and half of the participants smoked.

Table 2 presents data measured from the last follow-up and the change from baseline of blood glucose, blood pressure, and blood lipids for the entire study population between the different follow-up frequencies. The mean SBP and DBP levels were not significant (p = 0.053, p = 0.154). However, statistically significant differences in the changes of SBP and DBP between <4 times/year and ≥4 times/year follow-up visits were observed (p = 0.005, p = 0.000). As for blood glucose, the differences were statistically significant (p = 0.000, p = 0.000, p = 0.006, respectively). For LDL-C, there was a statistically significant difference between <4 times/year follow-up frequency and ≥4 times/year (p = 0.031) and the changes of LDL-C between these follow-up frequencies also had a statistically significant difference (p = 0.003).

The results showed the proportion of target-reaching in HbA1c, BP, and LDL-C in patients with different follow-up frequencies (Table 3). Participants who had follow-up frequency of 4 times/year had the highest proportion of target-reaching rate in all three variables, and 16.27% of patients met with all the targets. The follow-up frequency of 4 times/year was statistically significant in HbA1c and LDL-C (p < 0.05) compared with <4 times/year.

Regression analysis showed that ≥4 times/year follow-up frequency was associated with a higher OR of attainment of HbA1c goal than <4 times/year. The association between frequency of follow-up and the target-reaching rate in HbA1c remained significant (p < 0.05) after adjusting confounders (Table 4). There was no significant difference in the attainment of HbA1c goal between 4 times/year and >4 times/year follow-up groups.

Table 5 shows that ≥4 times/year follow-up frequency was associated with a higher OR of LDL-C than <4 times/year. The association between ≥4 times/year follow-up frequency and the target-reaching rate in LDL-C remained significant after adjustment for confounders (p = 0.000, p = 0.001).

Discussion

The ADA recommends the patients with T2DM to be followed up every 3–6 months, or 2–4 times annually [5]. Our studies found that compared with patients with a follow-up frequency of <4 times/year (2–3 times/year), patients with a follow-up frequency of 4 times/year or >4 times/year had a higher proportion of targets reached in HbAlc and LDL-C. However, >4 times/year follow-up had no additional benefits compared with 4 times/year, which suggested that the follow-up frequency of 4 times/year was most cost-effective to reach the maximum benefits for patients with T2DM.

In our study, with the increase in the frequencies of follow-up, the HbAlc levels reduced significantly. The same results were observed in other studies. Turkcan et al. [3] reported that follow-up appointments with care providers significantly reduced patients' HbAlc levels. In two randomized controlled studies [8, 9], the increase in the frequency of the follow-up was demonstrated to be effective in improving the HbA1c levels. Although these studies showed the beneficial effects of increasing the frequency of follow-up, they did not explore the optimal follow-up frequency on the target-reaching rate of HbA1c. Our study indicated that the follow-up frequency of 4 times/year had the maximum benefit in improving the HbA1c levels. A retrospective study [10] revealed that the frequency of follow-up was not associated with HbA1c levels in young T2DM patients. This could be attributed to the relatively small size (84) compared to

Table 1 Baseline characteristics of participants with different follow-up frequencies

Characteristics	Total ($N = 3035$)	1 time a year ($N = 1614$)	2 times a year ($N = 800$)	3 times a year ($N = 396$)	≥4 times a year ($N = 225$)	F/χ^2	p
Age (years)	56.08 ± 10.58	56.36 ± 10.93	56.47 ± 10.33	55.39 ± 9.88	53.87 ± 9.89	4.584	0.003
Duration of diabetes (years)	7.08 (1.33 10.83)	3.67 (1.08 9.67)	5.96 (1.08 9.67)	7.58 (2.38 12.94)	5.17 (2.25 11.50)	17.570	0.000
SBP (mmHg)	133 (120 145)	131 (119 143)	134 (122 148)	131 (119 145)	135 (126 147)	8.942	0.000
DBP (mmHg)	75 (68 82)	74 (68 81)	75 (67 82)	75 (68 82)	76 (70 85)	4.959	0.002
H (b/min)	80 (71 87)	79 (72 87)	78 (71 87)	77 (70 86)	79 (72 86)	1.354	0.255
BMI (kg/m^2)	25.46 ± 3.46	25.44 ± 3.49	25.43 ± 3.36	25.40 ± 3.43	25.91 ± 3.65	1.327	0.264
WHR	0.94 ± 0.16	0.94 ± 0.07	0.94 ± 0.07	0.96 ± 0.42	0.93 ± 0.63	3.025	0.028
SAT	178.9 (134.4 214.0)	173.6 (134.5 218.5)	172.2 (137.0 211.0)	168.1 (129.6 208.1)	166.7 (127.0 207.2)	0.643	0.587
FPG (mmol/L)	8.82 ± 3.56	8.89 ± 3.75	8.85 ± 3.44	8.53 ± 3.20	8.77 ± 3.18	1.113	0.343
2 hPG (mmol/L)	14.44 ± 5.91	14.45 ± 6.07	14.52 ± 5.79	14.14 ± 5.49	14.51 ± 5.84	0.389	0.761
HbA1c (%)	8.22 ± 2.10	8.23 ± 2.10	8.24 ± 2.19	8.16 ± 2.07	8.11 ± 1.84	0.340	0.796
FINS (mmol/L)	11.81 (5.40 13.40)	8.50 (5.60 13.00)	8.80 (5.30 13.93)	9.10 (5.20 13.80)	9.40 (5.20 14.68)	8.541	0.000
C-peptide (mmol/L)	2.28 ± 1.26	2.31 ± 1.18	2.31 ± 1.44	2.14 ± 1.17	2.21 ± 1.28	2.267	0.079
HDL-C (mmol/L)	1.26 ± 0.49	1.26 ± 0.46	1.28 ± 0.52	1.20 ± 0.29	1.24 ± 0.79	2.604	0.050
LDL-C (mmol/L)	2.87 ± 0.97	2.90 ± 0.98	2.88 ± 0.96	2.76 ± 0.98	2.77 ± 0.91	3.132	0.025
TC (mmol/L)	5.05 ± 1.29	5.10 ± 1.26	5.09 ± 1.33	4.91 ± 1.35	4.89 ± 1.16	3.636	0.012
TG (mmol/L)	1.86 (0.95 2.06)	1.38 (0.98 2.05)	1.37 (0.91 2.11)	1.30 (0.88 1.99)	1.36 (0.96 2.18)	0.313	0.816
Smoker, *n* (%)	1000 (32.9%)	593 (36.7%)	213 (26.6%)	129 (32.6%)	65 (28.9%)	8.964	0.000
Alcohol drinker, *n* (%)	1243 (50.0%)	678 (42%)	286 (35.8%)	173 (43.7%)	106 (47.1%)	4.833	0.002
Diabetic foot, *n* (%)	81 (2.7%)	40 (2.5%)	18 (2.3%)	16 (4.1%)	7 (3.1%)	1.312	0.269
Dyslipidemia, *n* (%)	763 (25.1%)	377 (23.4%)	214 (26.8%)	110 (27.8%)	62 (27.6%)	2.011	0.110
Hyperuricemia, *n* (%)	335 (11.7%)	173 (10.7%)	101 (12.7%)	53 (13.4%)	28 (12.4%)	1.146	0.329
Gout, *n* (%)	781 (25.7%)	677 (41.9%)	65 (50%)	32 (55.2%)	17 (60.7%)	3.584	0.013
CHD, *n* (%)	160 (5.3%)	105 (6.5%)	15 (6.4%)	30 (7.6%)	10 (4.4%)	0.780	0.505
Strock, *n* (%)	70 (2.3%)	45 (2.8%)	22 (2.8%)	2 (0.5%)	1 (0.4%)	3.853	0.009

(*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *H* heart rate, *BMI* body mass index, *WHR* waist-to-hip ratio, *SAT* subcutaneous adipose tissue, *FPG* fasting plasma glucose, *2 hPG* 2 h postprandial glucose, *HbA1c* hemoglobin A1c, *FINS* fasting serum insulin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride, *CHD* coronary heart disease, *p* value significance in < 0.05.)

Table 2 Changes in the metabolic values after 1-year care under MMC among participants with follow-up frequency <4 times/year, ≥4 times/year

		2 times/year (N = 800)	3 times/year (N = 396)	≥4 times/year (N = 225)	F/χ^2	p
SBP (mmHg)	After	129 (118 141)	127 (116 138)	127 (117 140)	2.941	0.053
	Change	−4.69 ± 15.94	−4.48 ± 17.50	−8.24 ± 16.57	10.777	**0.005**
DBP (mmHg)	After	73 (65 80)	71 (64 79)	73 (65 80)	1.876	0.154
	Change	−1.80 ± 8.55	−3.41 ± 9.74	−4.45 ± 9.82	21.254	**0.000**
FPG (mmol/L)	After	7.74 ± 2.81	7.56 ± 2.65	7.39 ± 1.86	37.756	**0.000**
	Change	−1.11 ± 3.57	−0.97 ± 3.41	−1.40 ± 3.50	1.838	0.399
2 hPG (mmol/L)	After	12.85 ± 5.01	12.68 ± 4.90	12.52 ± 4.52	24.076	**0.000**
	Change	−1.68 ± 6.19	−1.45 ± 6.06	−2.04 ± 6.25	0.625	0.732
HbA1c (%)	After	7.39 ± 1.46	7.31 ± 1.26	7.06 ± 1.21	5.114	**0.006**
	Change	−0.85 ± 1.87	−0.85 ± 1.84	−1.05 ± 1.76	1.718	0.424
HDL-C (mmol/L)	After	1.24 ± 0.33	1.24 ± 0.42	1.22 ± 0.31	0.232	0.793
	Change	−0.04 ± 0.47	0.05 ± 0.36	−0.01 ± 0.76	20.458	**0.000**
LDL-C (mmol/L)	After	2.58 ± 1.46	2.58 ± 0.87	2.34 ± 0.80	3.469	**0.031**
	Change	−0.30 ± 1.53	−0.18 ± 0.95	−0.42 ± 0.97	11.726	**0.003**
TG (mmol/L)	After	1.25 (0.86 1.82)	1.27 (0.86 1.96)	1.28 (0.87 1.83)	0.235	0.791
	Change	−0.36 ± 3.34	−0.13 ± 3.80	−0.22 ± 2.28	1.028	0.598

(*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *2 hPG* 2 h postprandial glucose, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, significant values ($p < 0.05$) are shown in bold.)

our study. However, their participants were adolescents (mean age, 13.6) who were under pressure and facing psychosocial issues. Another study showed psychiatric disorders to be one of the most protruding barriers while treating adolescents with T2DM [11]. On the contrary, the average age of the patients in our study was 56, with the risk of chronic complications, which may motivate them to control their diabetes. Furthermore, most patients in our study were retired and had more time to manage their diseases.

Table 3 Proportion of the targets attained for HbA1c, BP, and LDL-C levels in patients with different follow-up frequencies

	HbA1c	BP	LDL-C	All targets met
<4 times (2–3times)/year (N = 1196)	48.49%	47.24%	54.77%	12.54%
=4 times/year (N = 166)	51.20%*	51.20%	65.06%*	16.27%
>4 times/year (N = 59)	50.85%	40.68%	72.88%	10.17%
Total (N = 1421)	48.91%	47.43%	56.72%	12.88%

* Significant difference between <4 times (2–3times)/year and =4 times/year ($p < 0.05$)

HbA1c hemoglobin A1c, *BP* blood control, *LDL-C* low-density lipoprotein cholesterol

Dyslipidemia is one of the major risk factors for cardiovascular disease in hyperglycemic patients, which leads to death [12]. Therefore, it is necessary to manage lipid levels. Our study found that 4 times/year follow-up visits were the most appropriate for controlling blood lipids in patients with diabetes. Only a few studies have explored the relationship between the frequency of follow-up and the target-reaching rate of LDL-C in T2DM patients. Similarly, there is a lack of investigation to determine the optimum follow-up frequency for diabetic patients with lipid control. It was worth noting that our study demonstrated that the LDL-C improved with the increase of follow-up frequency and 4 times/year follow-up frequency could achieve the maximum benefit of controlling LDL-C and >4 times/year did not bring additional benefits. Chinese Adult Guidelines for The Prevention and Treatment of Blood Lipid recommended measurement of blood lipid levels in patients with diabetes along with CVD every 3–6 months, that is, 2–4 times annually [13]. From the perspective of our study, we confirmed that patients with T2DM annually followed up 4 times with clinical specialists could control HbA1c and LDL-C levels effectively.

Our study found that increased follow-up frequency was significant for decreasing BP, and the degree of BP reduction was also higher. This was consistent with the previous literature [14]. However, we did not observe the relationship between the target-reaching rate of BP and the frequency of

Table 4 Logistic regression analysis of different follow-up frequencies associated with the target-reaching rate in HbA1c

Follow-up frequency(times/year)	Model 1			Model 2			Model 3		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
<4		1							
=4	1.563	(1.142–2.138)	0.005	1.603	(1.162–2.210)	0.004	1.518	(1.097–2.100)	0.012
>4	1.655	(1.205–2.274)	0.002	1.625	(1.178–2.240)	0.003	1.508	(1.088–2.089)	0.014

Model 1: crude OR

Model 2: adjusted for sex, age, BMI, smoking, alcohol consumption, duration of T2DM, use of statins, and use of insulin

Model 3: adjusted for sex, age, BMI, smoking, alcohol consumption, duration of T2DM, use of statins, use of insulin, DBP, SBP, HDL-C, and LDL-C

follow-up. Current studies do not provide sufficient information to conclude the optimal relationship of the follow-up frequency and the target-reaching rate of BP, and further research is needed.

Under the management of MMC, our study showed that 48.91% of these patients met HbA1c < 7%, 56.72% of them achieved LDL-C < 2.6 mmol/L, and 47.73% reached BP < 130/80 mmHg. The three combined therapeutic targets were achieved in 12.88% patients after a 1-year follow-up, which doubled from baseline (6.33%). The proportion of targets reached in HbA1c, LDL-C, and BP was higher than two nationwide multi-center cross-sectional studies [6, 15] conducted in China, in which the proportion of targets reached in HbA1c, blood lipids, BP, and all three target goals were 35.2–47.7%, 36.1–45.1%, 28.4–35.5%, and 5.4–5.6%, respectively. Similarly, the total target-reaching rate of our study was higher than that of an earlier German study [16] (11.4%), with the same target-reaching requirements, and the rate of HbA1c, BP, and LDL-C in our study increased by 16.01%, 32.53%, and 28.42%, respectively, compared to their study. It showed that patients who received MMC care could achieve a higher level of target-reaching rate of HbA1c, BP, and LDL-C. MMC has advanced medical equipment and systematic care. Moreover, patients receive a one-stop service with a conducive and precise mode of care, and screening of complications [7]. Our study suggested that MMC is a useful care model to help Chinese patients with T2DM in controlling blood glucose, blood pressure, and blood lipids.

This study had several limitations. The primary limitation was the use of medical data from a single healthcare system, which limited the generalizability of the findings, as treatment patterns might vary by system and region. Besides, as an observational study, selection bias could not be completely avoided. However, bias in data quality and integrity is controlled. On the one hand, the data included in this study were all from an independent digital medical record system established by MMC. All follow-up data were collected retrospectively and did not rely on the recollections of patients or their families. On the other hand, all patients retained valid information, ensuring the authenticity and integrity of data and reducing selection bias and information bias.

Conclusion

Our study indicated that MMC is a useful model to improve the metabolic target-reaching rate of diabetes patients in China with the follow-up frequency of 4 times/year being optimal and cost-effective measure.

Table 5 Logistic regression analysis of different follow-up frequencies associated with the target-reaching rate in LDL-C

Follow-up frequency(times/year)	Model 1			Model 2			Model 3		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
<4		1							
=4	2.189	(1.578–3.037)	0.000	2.194	(1.576–3.054)	0.000	1.998	(1.433–2.786)	0.000
>4	2.678	(1.531–4.684)	0.001	2.675	(1.523–4.698)	0.001	2.517	(1.428–4.436)	0.001

Model 1: crude OR

Model 2: adjusted for sex, age, BMI, smoking, alcohol consumption, duration of T2DM, use of statins, and use of insulin

Model 3: adjusted for sex, age, BMI, smoking, alcohol consumption, duration of T2DM, use of statins, use of insulin, DBP, SBP, FPG, and 2 hPG

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Author contribution Study conception and design: QDZ and CYX
Data collection: QDZ, JHL, and XQL
Data analysis and interpretation: YW and ML
Drafting of the article: JHL and XQL
Critical revision of the article: CYX and QDZ
All of the authors approved the final version and agreed to be accountable for all aspects of the work.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval It was approved by the Ethical Committee of Health Community Group of Yuhuan Second People's Hospital. Participants provided written informed consent before enrollment.

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ORIGINAL ARTICLE

Utilization of statins in patients with type 2 diabetes mellitus: the practice in a lower middle income South Asian country

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Abstract

Background Cardiovascular disease (CVD) is a major cause of morbidity and mortality among patients with type 2 diabetes. Statin reduces CVD risk. The ACC/AHA 2018 guideline on dyslipidemia recommends all patients with type 2 diabetes mellitus to be given moderate-intensity statin. We aimed to determine the prescription practices of statins among patients with type 2 diabetes mellitus.

Methods A cross-sectional study was conducted from February to April 2021. Patients with type 2 diabetes mellitus between 40 and 75 years were recruited from the University Medical Clinic and Endocrine Clinic at Colombo South Teaching Hospital, Sri Lanka.

Results Four hundred seventy-one patients were enrolled with a mean age of 59.05 (± 9.139) years. The mean duration of diabetes was 10.97 (± 9.57) years. Four hundred forty-one (93.6%) patients were on statin and 30 (6.4%) patients were not on statin therapy. Those not on statins were not prescribed statins.

Conclusions There were 163 (34.61%) patients who required high intensity. Though only 3 (1.73%) were on high-strength statin, the rest were on moderate (152, 93.25%), low (4, 2.45%), and none (4, 2.45%). Among patients with prior history of atherosclerotic cardiovascular disease (ASCVD) and the high-risk category according to the 10-year ASCVD risk estimation (155, 32.91%), only 17 (10.97%) have achieved optimal LDL therapeutic targets (55mg/dL). A large proportion of the study population received statin therapy for primary and secondary prophylaxis. However, the majority were on suboptimal doses of statin and have not achieved therapeutic targets with regard to LDL-C levels. The findings highlight the importance of improving statin therapy and optimizing lipid management according to evidence-based guideline recommendations.

Keywords Statin · Type 2 diabetes mellitus · Sri Lanka · South East Asia · Atorvastatin · Rosuvastatin · Audit · Dyslipidemia · Lipid

Background

Cardiovascular disease (CVD) affects nearly one-third of the population and currently, it is a major cause of mortality worldwide [1]. According to the 2018 World Health Organization Non-communicable Diseases (NCD) Country Profiles, 83% of deaths in Sri Lanka are caused by NCD and 34% of the total mortality was due to cardiovascular disease (CVD). The prevalence of diabetes mellitus is increasing in Sri Lanka. Local studies show that one out of five adults in Sri Lanka has either diabetes mellitus or pre-diabetes [2].

Apart from lifestyle modifications, optimal pharmacotherapy plays a pivotal role in achieving therapeutic targets in the reduction of associated morbidity and mortality diabetes [3]. Statins are one such drug that has shown to be beneficial in large-scale trials and recommended in current guidelines in patients with type 2 diabetes mellitus (T2DM). Each 1 mmol/L (38.7 mg/dL) lowering in LDL-C reduced the mortality and major adverse cardiovascular events by 0.80 (95% CI, 0.77–0.83), consistently in both primary and secondary prevention [4]. The 2018 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease recommends

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the use of moderate-intensity statin in type 2 diabetes mellitus who are 40–75 years old [5]. The American Diabetes Association (ADA) published the standards on medical care for patients with type 2 diabetes, which includes recommendation for initiating lipid-lowering therapy and prescription of moderate-intensity statins for those with no additional risk factors, and high-intensity statins for those with either CVD risk factors or overt CVD. Although guidelines emphasize the remarkable value of statin in primary and secondary prevention of CVD, little is known about the prescription pattern of statin in Sri Lanka. Using a large cohort of patients, the present study focused on statin eligibility based on ACC/AAHA 2018 guidelines and patient characteristics associated with receiving statin therapy in patients with type 2 diabetes.

Methods

Study design

We conducted a cross-sectional study from February to April 2021 among patients with type 2 diabetes mellitus attending the University Medical Clinic and Endocrine Clinic at Colombo South Teaching Hospital, Sri Lanka. This is one of the largest tertiary care hospitals in the country.

Data source and patient selection

Patients with diabetes between 40 and 75 years were recruited and type 1 diabetes mellitus patients, immunocompromised patients, and pregnant women were excluded. The study was conducted using a data extraction sheet which recorded the demographic data and clinical parameters and the investigations (FBS, serum creatinine, HbA1C, and lipid profile).

The latest investigations available within 1 year were taken into account. Data was analyzed using IBM SPSS version 21. Nominal variables were presented as the number of cases and percentages, and continuous variables were presented as means ± standard deviations. Comparison of clinical and demographic factors by gender and statin use was achieved by using the chi-square or Fisher's exact tests for categorical variables. The significance level was set at $p < 0.05$.

Statin eligibility criteria

Statin treatment regimens of the study groups were compared with the treatment recommendations of 2018 ACC/AHA guidelines.

Definitions of variables

Demographics

Education up to grade five and above grade five was considered as primary education and secondary education, respectively.

Comorbidities

The diagnosis of hypertension was based on the self-reported history of hypertension, documentation on clinic records, and the use of hypertension-lowering medications or sustained blood pressure ≥ 140/90 mmHg in more than one visit. We considered CVD as coronary artery disease (CAD), CVA (ischemic strokes, transient ischemic strokes), and peripheral arterial disease (PAD). CAD was any documented definite or probable myocardial infarction, CAD-related revascularization (surgery, angioplasty, stenting, or any combination of these), or stable angina in participants' medical records. Data on CVA and PDA were extracted from participants' medical records as defined by the treating physician. Smoking status was a documented self-report of current smoking habits. History of dyslipidemia was obtained by patients' medical records. We estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD), and classified patients with eGFR < 60 ml/min/1.73 m^2 as having CKD. Dipstick proteinuria appeared as negative (−), trace, (+), (++), or (+++) in the dataset. Individuals with ≥ (+) dipstick proteinuria results were considered as having nephropathy.

Cardiovascular risk and statin therapy

We estimated 10-year cardiovascular risk of the patients using ASCVD risk estimator plus and categorized them as low (< 5%), borderline (5 to < 7.5%), intermediate (≥ 7.5 to < 20%), and high (≥ 20%). All patients with type 2 DM were considered as statin eligible. Intensity of statin therapy was defined according to the ACC/AHA 2018 guideline. Atorvastatin 40–80 mg and rosuvastatin 20–40 mg were defined as high-intensity statin therapy and atorvastatin 10–20 mg and rosuvastatin 5–10 mg were defined as moderate-intensity statin therapy. Prescription of statin for patients with previous documented CVD was considered as secondary prevention and the rest as for primary prevention. Statin use was measured based on the prescription records during the patients' clinic follow-up as all records at CSTH were not computerized.

Results

Basic characteristics

Four hundred seventy-one type 2 diabetes mellitus patients were enrolled. The mean age of the study population was 59.05 (± 9.139) years. Three hundred fourteen (66.7%) were female and 157 (33.3%) were male. The mean diabetic duration was 10.97 (± 9.57) years with 243 (51.6%) patients having type 2 diabetes mellitus over 10 years.

Among the participants, the cardiovascular risk factors detected were hypertension in 333 (70.7%), dyslipidemia in 115 (24.4%), and smoking in 8 (1.7%). Chronic kidney disease (CKD) was detected in 114 (24.2%) patients and 126 (26.8%) had nephropathy. However, albuminuria was not investigated in 288 (61.1%) patients. Macrovascular complications of diabetes were reported in 60 (12.74%) patients: coronary artery disease in 55 (11.7%), peripheral vascular disease in 4 (0.8%), and cerebrovascular disease in 9 (1.9%).

An overview of the main characteristics of the study population is summarized in Table 1.

Table 1 Main characteristics of the study population

Characteristics	Frequency (*n*)	Percent (%)
Gender		
Female	314	66.7
Male	157	33.3
Duration of diabetes		
< 10 years	228	48.4
≥ 10 years	243	51.6
Educational status		
≤ Primary education	68	14.4
≥ Secondary education	360	76.4
N/A	43	9.1
Hypertension		
Yes	333	70.7
No	138	29.3
Dyslipidemia		
Yes	115	24.4
No	356	75.6
Smoking		
Yes	8	1.7
No	463	98.3
Atrial fibrillation		
Yes	3	0.6
No	468	99.4
Rheumatoid arthritis		
Yes	7	1.5
No	464	98.5
Nephropathy		
Yes	126	26.8
No	57	12.1
N/A	288	61.1
CKD		
Yes	114	24.2
No	357	75.8
IHD		
Yes	65	13.8
No	406	86.2
PVD		
Yes	5	1.1
No	466	98.9
Stroke		
Yes	10	2.1
No	461	97.9
ASCVD category		
Low	160	34
Borderline	37	7.9
Intermediate	109	23.1
High	94	20.0
Established ASCVD	71	15.1

Characteristics of statin therapy

Statins were prescribed for 441 (93.6%) patients. Thirty (6.4%) patients were not on statin therapy. Out of the patients who were on statin, 60 (13.61%) were prescribed statins for secondary prevention and 381 (86.39%) for primary prevention. The most frequently prescribed statin therapy was atorvastatin (97.28%) followed by rosuvastatin (2.72%).

In relation to the statin-non-prescribed group, the statin-prescribed group was more likely to be hypertensive (43.33% vs 72.56%; $p = 0.001$), more likely to have dyslipidemia (6.67% vs 25.62%; $p = 0.019$), and likely to have a history of ischemic heart disease (0% vs 12.47%; $p = 0.040$). Factors associated with statin prescription are summarized in Table 2. A log-binomial model was fitted to examine the adjusted associations between statin prescription and various factors among the diabetic patients in the study. The best fit resulted with the covariates displayed in Table 3. Diagnosis of hypertension, borderline, and high-risk ASCVD groups were found to be associated with an increased likelihood of receiving statin therapy.

In our study, there were 60 (15.1%) patients with prior history of atherosclerotic cardiovascular disease (ASCVD), 8 (1.7%) patients LDL level ≥ 190 mg/dL, and 95 (20.2%) patients with 10-year cardiovascular risk > 20% requiring high-intensity statin therapy according to the 2018 ACC/AHA guideline on the management of blood cholesterol. Out of them, only 3 (1.73%) were prescribed with high-intensity statins. The rest were prescribed with moderate-intensity (152, 93.25%) and low-intensity (4, 2.45%) statins. Four patients (2.45%) were not given statins. The statin prescription pattern in study population is summarized in Figure 1.

Table 2 Factors associated with statin prescription among statin-eligible patients with type 2 diabetes ($N = 471$)

Characteristics	Subcategory	Statin not prescribed ($n = 30$)	Statin prescribed ($n = 441$)	p value
Gender	Females	21 (70.00%)	293 (66.44%)	0.689
	Males	09 (30.00%)	148 (33.56%)	
Age	40–64 years	24 (80.00%)	295 (66.89%)	0.137
	65–75 years	06 (20.00%)	146 (33.11%)	
Clinic	Endocrine	30 (100.00%)	435 (98.64%)	0.520
	Medical	00 (0.00%)	06 (1.36%)	
Education status	≤ Primary education	03 (10.00%)	65 (14.74%)	0.589
	> Primary education	23 (76.67%)	337 (76.42%)	
	NA	04 (13.33%)	39 (8.84%)	
Duration of diabetes	< 10 years	19 (63.33%)	209 (47.39%)	0.091
	≥ 10 years	11 (36.67%)	232 (52.61%)	
Hypertension	Yes	13 (43.33%)	320 (72.56%)	0.001
	No	17 (56.67%)	121 (27.44%)	
Dyslipidemia	Yes	02 (6.67%)	113 (25.62%)	0.019
	No	28 (93.33%)	328 (74.38%)	
Smoking	Yes	00 (0.00%)	08 (1.81%)	0.457
	No	30 (100.00%)	433 (98.19%)	
CKD	Yes	05 (16.67%)	109 (24.72%)	0.319
	No	25 (83.33%)	332 (75.28%)	
Nephropathy	Yes	04 (13.33%)	122 (27.66%)	0.210
	No	05 (16.67%)	52 (11.79%)	
	NA	21 (70.00%)	267 (60.54%)	
IHD	Yes	00 (00.00%)	55 (12.47%)	0.040
	No	30 (100.00%)	386 (87.53%)	
PVD	Yes	00 (00.00%)	04 (0.91%)	0.600
	No	30 (100.00%)	437 (99.09%)	
Stroke	Yes	00 (00.00%)	09 (2.04%)	0.430
	No	30 (100.00%)	432 (97.96%)	
ASCVD	Low	14 (46.67%)	152 (34.47%)	0.119
	Borderline	04 (13.33%)	33 (7.48%)	
	Intermediate	08 (26.67%)	105 (23.81%)	
	High	04 (13.33%)	91 (20.63%)	
	Previous	00 (0.00%)	60 (13.61%)	

Table 3 Adjusted relative risks for associations between various factors and statin prescription

Characteristics	Risk ratio	95% CI	p value
Sex (male)	1.0028777	0.9661957–1.0409524	0.87986
Age	1.0002212	0.9973583–1.0030923	0.87981
Duration of diabetes	1.0003480	0.9997019–1.0009946	0.29120
CKD	1.0006030	0.9942884–1.0069576	0.85196
Dyslipidemia	1.0282467	0.9345710–1.1313118	0.56763
Hypertension	1.1011756	1.0034628–1.2084033	0.04206
Smoking	1.0040577	0.9968161–1.0113519	0.27287
ASCVD—borderline	0.9747494	0.9747494–0.9747494	0.00029
ASCVD—intermediate	1.0439577	0.9672446–1.1267551	0.26928
ASCVD—high	1.0226453	1.0226453–1.0226453	0.00057
Previous ASCVD	1.0498369	0.9520481–1.1576699	0.32960

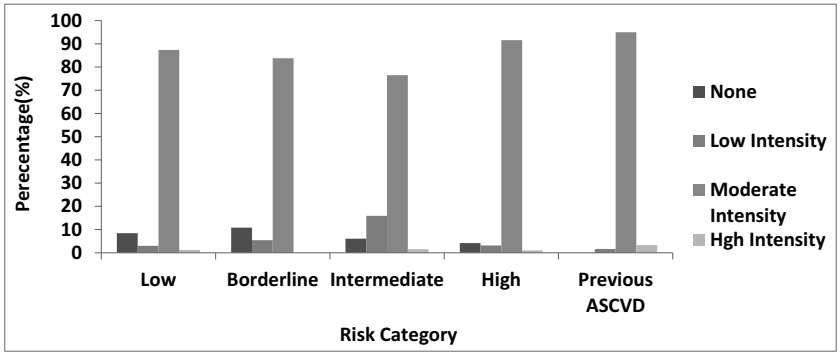

Fig. 1 Prescription of statin: Intensity vs risk category

LDL therapeutic target achievement

In further analysis of patients with prior history of ASCVD and high-risk category according to the 10-year ASCVD risk estimation, only 17 (10.97%) have achieved optimal LDL therapeutic targets.

Reasons for non-prescription of statins

All 30 patients who were not on statins were patients who should have been prescribed statins for primary prevention. Only patients who needed primary prevention were not prescribed statin. Side effects due to statin, drug interactions, and non-compliance were assessed as causes for not prescribing statins. None of the patients who were not on statins was not prescribed due to the above causes. The patients who were not prescribed statins were not aware that they should have been prescribed a statin. None of the patients who were not on statins had discontinued statin, nor intolerant or had contraindications for statins.

Discussion

This study was based on the current evidence for statin prescription. A significant proportion of our study population received statin therapy which is commendable. An observational cohort study conducted to evaluate the global pattern of comprehensive cardiovascular risk factor management with type 2 diabetes patients reported that only 48.5% of South Asians were prescribed with statin [6]. In a multicenter study conducted in India, similar results of only 55.2% were prescribed statin [7]. The statin prescription rate in our study was much higher. Sri Lanka is a resource-poor country similar to India. The Sri Lankan health system is free for all in the state sector. The high adherence to statin prescription for all type 2 diabetes patients is noteworthy. The statins were prescribed preferably for diabetics with IHD and hypertension. This indicated the clinicians understand the CVD risk factors in diabetes as the presence of these risk factors enhances the risk in patients with diabetes. The fact that should be promoted as knowledge is that all diabetics require statins and not just the ones with high CVD risk.

Under-prescription of statin in our population is a major concern as statin therapy is associated with a measurable reduction of cardiovascular mortality and morbidity at a low cost. All the patients who were not on statins in our study were not on them as the prescribers have not prescribed them. As a country with universal free health care, prevention of type 2 diabetes mellitus–related cardiovascular morbidity is cost-effective. In previous studies, the reason practitioners did not prescribe lipid-lowering agents in patients with type 2 diabetes has been related to patient factors and physician factors. Patient factors included compliance issues or refusal due to expected or perceived side effects. Physician factors included, patients not at high risk, patients at treatment targets, short life expectancy, and expected compliance issues [8, 9].

Despite the high prescription rate of statin, majority of the patients were on suboptimal doses. A majority who should be on high doses were prescribed with moderate-intensity statin. The statin intensity makes a difference in the achievement of LDL goals. The LDL reduction is proportionate to the intensity of statins. The fact that patients who should have been started on high intensity have been given only moderate intensity is discouraging. Steinberg et al. found that statins are under-dosed frequently in day-to-day clinical practice [10]. In another study done in India, a low prescription rate of high-strength statins (12.7%) was seen which is consistent with our findings [7]. Lack of sensitivity to contemporary evidence-based recommendations and individual perspectives of possible side effects of statin such as muscle toxicity strengthened by the paucity of population-based evidence could have affected the substandard prescription pattern and low level of therapeutic target accomplishment. Several studies done in Sri Lanka have shown side effects of stains to be minimal [11]. Therefore, statins at the appropriate intensity should be prescribed to patients. This requires further education of the clinicians to encourage them to use high-intensity statins when clinically indicated.

None of the patients in the study was not given high-intensity statin due to side effects. This requires further

education of the clinicians to encourage them to use high-intensity statins when clinically indicated.

A notable proportion, even among the patients who needed secondary prevention of CVD and high-risk 10-year ASCVD category have not achieved the therapeutic goals. The importance of checking lipid profiles regularly and optimizing statin therapy adding on therapy such as ezetimibe to reach LDL goals needs to be emphasized. A study conducted to estimate control of modifiable risk factors in diabetes patients in primary care setting and attainment of therapeutic goals of LDL-C levels in routine clinic practice in a tertiary care setting in Sri Lanka reported low-level achievement of therapeutic goals. Only 24.3% and 12.9% have achieved the therapeutic target in those studies respectively which is compatible with our findings [13, 14]. The reason for not achieving LDL goals could be unawareness of the importance of reaching goals among the prescribers. Analysis of statin non-prescribed group and non-achievement of therapeutic goals is suggestive of clinical inertia. However, further evaluation of root causes for the gap between clinical practice and the current guidelines needs further studies of qualitative nature to understand the prescribing practice of the doctors.

Conclusion

In conclusion, this study shows that despite the high rate of statin utilization, prescription of the right intensity of statin according to the risk category is substantially far below the current recommendations.

Limitations

There are several limitations of this study. The study was done in a single center and this was carried out during the 3rd wave of the COVID-19 pandemic, limiting patients' clinic attendance and the number of investigations done during the period of the study.

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Author contribution ATM was involved in conceptualization, methodology, validation, writing—reviewing and editing, and supervision. PDJK was involved in investigation, data curation, and writing of the manuscript. GS was involved in formal analysis of the data. CG was involved in patient management. All authors critically reviewed and approved the final version.

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Availability of data and materials The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Permission to carry out the study received from the Institution: Colombo South Teaching Hospital, Sri Lanka.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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ORIGINAL ARTICLE

Effect of stress hyperglycemia on admission and glycosylated hemoglobin on left ventricular function and inflammatory factors in patients with diabetes mellitus combined with myocardial infarction undergoing PCI

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Abstract

Purpose In this study, we analyzed the effect of stress hyperglycemia on patients admitted with diabetes mellitus. The effects of glycated hemoglobin (HbA1c) on left ventricular function and inflammatory factors in these patients with diabetes mellitus and myocardial infarction undergoing percutaneous coronary intervention (PCI) were also studied.

Methods The clinical data of 160 patients with diabetes mellitus and myocardial infarction treated with PCI over the period of December 2018 to June 2020 were retrospectively analyzed. The patients were divided into groups A (38 cases), B (40 cases), C (43 cases), and D (39 cases) according to their blood glucose (AG) and HbA1c levels upon admission.

Results The levels of FGB, 2hPG, and HbA1c in group B after PCI were significantly higher than those in groups A, C, and D ($p < 0.05$). After PCI, group B showed significantly higher levels of LVESD and LVEDD and significantly lower levels of LVEF than other groups ($p < 0.05$). The levels of TNF-α, IL-6, and CRP in group B after PCI were significantly higher than those in other groups ($p < 0.05$). The incidence of endpoint events was higher in group B (35.00%) than in the other three groups ($p < 0.05$). Multiple logistic regression analysis indicated that high AG and HbA1c levels were the main risk factors for adverse prognosis ($p < 0.05$). AG and HbA1c were positively correlated with LVESD, LVEDD, TNF-α, IL-6, and CRP levels, and negatively correlated with LVEF levels ($p < 0.05$).

Conclusions In summary, in patients with diabetes mellitus combined with myocardial infarction and undergoing PCI on admission, stress hyperglycemia and high HbA1c levels were associated with higher FGB and 2hPG levels, which exacerbate ventricular functional impairment and inflammatory response, increase the risk of endpoint events, and can be predictors of patient prognosis.

Keywords Diabetes mellitus combined with myocardial infarction · Stress hyperglycemia · Glycated hemoglobin · Left ventricular function · Inflammatory factors

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Introduction

Myocardial infarction is a cardiovascular disease with a high incidence and often accompanied by diabetes mellitus, which increases the complexity of treatment [1, 2]. A state of hyperglycemia upregulates the expression of vascular endothelial growth factor and releases large quantities of inflammatory factors, which impair endothelial function and lead to decreased endothelial diastolic function. Hyperglycemia also increases endothelin activity, enhances vasoconstriction, and promotes the gene expression of chemokines and adhesion factors, resulting in increased formation of atheromatous plaque [3]. Ventricular remodeling after myocardial infarction produces an adaptive response, resulting in dilated and thinner myocardial blood vessels, increased myocardial load, and a continuous decrease in ventricular systolic function, which ultimately causes a reduction in myocardial oxygen supply [4]. Therefore, patients with myocardial infarction combined with diabetes mellitus face greater complications and experience a higher degree of myocardial injury, resulting in a poor prognosis following percutaneous coronary intervention (PCI).

Stress hyperglycemia is a pathophysiological response whereby elevation of blood glucose occurs during periods of stress such as illness, and patients with myocardial infarction often experience this condition [5] during an acute onset. Studies have shown [6] the occurrence of stress hyperglycemia in up to 25–50% of patients with acute myocardial infarction. As a part of the stress response, stress hyperglycemia causes a series of physiological reactions, such as sympathetic system excitation, accelerated respiration, and accelerated heart rate, worsening the condition of patients, with HbA1c being a crucial indicator of the blood glucose level [7]. Reportedly, stress hyperglycemia not only is related to the severity of an acute heart attack but also is an independent risk factor leading to poor prognosis [8]. The aim of this study was to analyze the effects of stress hyperglycemia and HbA1c on left ventricular function and inflammatory factors in patients undergoing PCI.

Material and methods

Baseline data

The clinical data of 160 patients with diabetes mellitus combined with myocardial infarction who had undergone PCI in our hospital between December 2018 and June 2020 were retrospectively analyzed. The patients were divided into groups A ($N = 38$), B ($N = 40$), C ($N = 43$), and D ($N = 39$) according to AG and HbA1c levels on admission. Group A: AG < 120 mg/dL and HbA1c < 6.5%; group B: AG ≥ 120 mg/dL and HbA1c < 6.5%; group B: AG < 120 mg/dL and HbA1c < 6.5%; group B: AG < 120 mgdL and HbA1c < 6.5%.

Inclusion criteria

Patients needed to meet the diagnostic criteria in the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2017 edition) [9] and the 2014 Expert Consensus on the Integrated Chinese and Western Medicine Treatment of Acute Myocardial Infarction [10]; be admitted within 24 h of its onset; and exhibit requirement for PCI surgery to be included in the study. Patients with coagulation dysfunction, combined malignancy, and a history of contraindication to surgery; on glucocorticoids before admission; who exhibited inflammatory response and infection before admission; who received anti-infection treatment; and with severe liver and kidney function abnormalities were excluded. The Ethics Committee of our hospital approved this study. The research subjects and their families were informed, and they signed a comprehensive consent form.

Methods

All patients received 300 mg of clopidogrel (J20180029, Sanofi (Hangzhou) Pharmaceutical Co., Ltd.) and 300 mg of aspirin (J20130078, Bayer Healthcare Ltd.) orally before PCI. Coronary angiography was performed using the Judkins method. The left radial artery was punctured using the Seldinger method, following which PCI was performed. Clopidogrel 75 mg/day with aspirin 100 mg/day was given for a period after the PCI.

Outcome measurement

(1) Ventricular function—Patient's ventricular function was evaluated using GE Vivid E9 echocardiography, covering left ventricular ejection fraction (LVEF), left ventricular end-systolic internal diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD).
(2) Inflammatory factors—The peripheral venous blood was collected (4 mL) and centrifuged to obtain the serum. Tumor necrosis factor (TNF-α) levels were measured by double antibody sandwich enzyme-linked immunosorbent assay, interleukin-6 (IL-6) levels were measured by radioimmunoassay, and C-reactive protein (CRP) levels were measured by immuno-scattering turbidimetric assay. The kits were purchased from the Shanghai Jinma Experimental Equipment Co.
(3) Endpoint events—All-cause mortality and the incidence of non-fatal myocardial infarction and other MACE endpoint events were recorded.
(4) Blood glucose index—The venous blood was drawn (2 mL), from it the fasting blood glucose (FBG), 2h

postprandial blood glucose (2hPG), and HbA1c were measured using a glucose analyzer.

Statistical analysis

Data were processed using SPSS 23.0. The measurements were expressed as $\chi \pm S$, and the one-way ANOVA test was used for comparison among multiple groups. The count data were expressed as percentages, and the regression analyses of AG, HbA1c, and prognosis were performed through multivariate logistic regression analysis. The correlation between AG, HbA1c, and ventricular function and inflammatory factors was analyzed using the bivariate Pearson correlation and examined using a χ^2 test. $p < 0.05$ was considered a statistically significant difference.

Results

Comparison of baseline data

There were no significant differences in age, sex (male/female), BMI, course of diabetes, time from onset to PCI, and site of myocardial infarction (anterior wall/inferior wall/anterior lateral wall/anterior interstitial wall) among the four groups ($p > 0.05$). Therefore, the data of patients in the four groups were comparable (Table 1).

Comparison of blood glucose indexes

After PCI, the levels of FBG, 2hPG, and HbA1c in group B were significantly higher than those in groups A, C, and D ($p < 0.05$). The remaining three groups were in the following order: group C > group D > group A ($p < 0.05$), suggesting that patients with diabetes mellitus combined with myocardial infarction undergoing PCI who had stress hyperglycemia and high HbA1c levels upon admission also exhibited higher FGB and 2hPG levels after PCI (Figure 1).

Comparison of left ventricular function

After PCI, group B showed significantly higher levels of LVESD and LVEDD and significantly lower levels of LVEF than groups A, C, and D ($p < 0.05$); among the remaining three groups, the levels of LVESD and LVEDD were in the order group C > group D > group A, whereas the levels of LVEF were in the order group C < group D < group A ($p < 0.05$), suggesting that the presence of stress hyperglycemia with high HbA1c levels in patients with diabetes mellitus combined with myocardial infarction upon admission and undergoing PCI exacerbates ventricular functional impairment (Figure 2).

Comparison of inflammatory factors

After PCI, the levels of TNF-α, IL-6, and CRP in group B were significantly higher than those in groups A, C, and D; among the remaining three groups, the levels of TNF-α, IL-6, and CRP were highest in group C, followed by group D, and lowest in group A ($p < 0.05$), suggesting that the presence of stress hyperglycemia and high HbA1c levels in patients with diabetes mellitus combined with myocardial infarction on admission and undergoing PCI exacerbates the inflammatory response (Figure 3).

Comparison of endpoint events

The incidence of endpoint events was higher in group B (35.00%) than in the other three groups ($p < 0.05$), suggesting that high stress hyperglycemia combined with high HbA1c levels upon admission increases the risk of endpoint events (Table 2).

Regression analysis of AG and HbA1c on prognosis

Using adverse prognosis (endpoint event) as the independent variables, and AG and HbA1c as the dependent variables, multiple logistic regression analysis yielded that high AG and HbA1c levels were the main risk factors for an adverse

Table 1 Comparison of baseline data ($\chi \pm S$/%)

Group	Group A (n=38)	Group B (n=40)	Group C (n=43)	Group D (n=39)	F/χ^2	p
Age (years)	51.08±7.42	50.42±7.17	52.61±7.65	52.18±7.47	0.729	0.536
Gender (m/f)	23/17	25/15	23/17	21/19	1.261	0.738
BMI (kg/m^2)	21.05±2.39	21.58±2.67	20.97±2.32	21.84±2.36	1.181	0.319
Duration of diabetes (years)	11.62±2.41	11.87±2.50	12.05±2.67	11.38±2.36	0.553	0.647
Time from onset to PCI (h)	6.48±1.36	6.71±1.45	7.09±1.68	6.90±1.57	1.180	0.319
Site of myocardial infarction (anterior wall/inferior wall/anterior lateral wall/anterior interstitial wall)	16/12/10/6	14/10/11/9	16/9/12/7	13/13/10/8	2.289	0.986

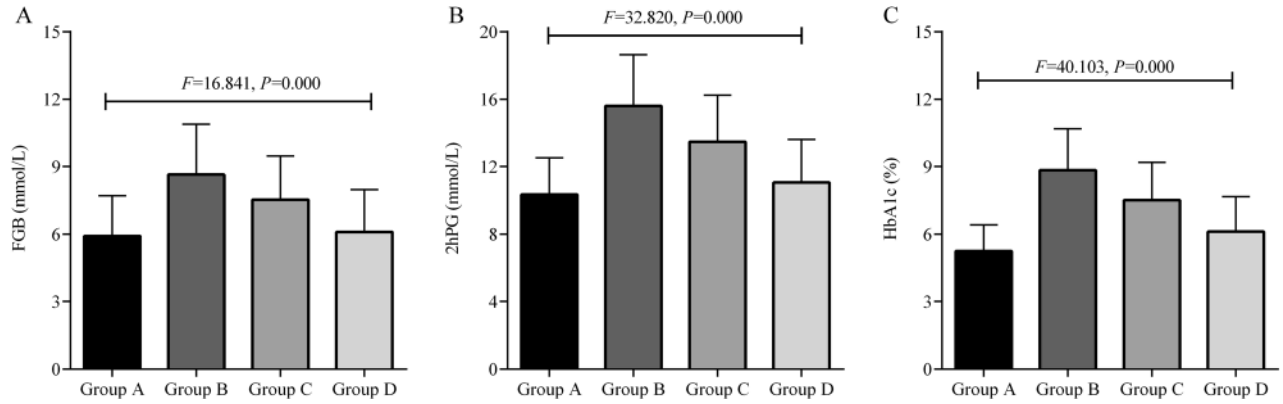

Figure 1 Effect of high stress hyperglycemia and glycated hemoglobin on blood glucose levels**.** Note: **A** higher FGB levels after PCI, **B** higher 2hPG levels after PCI, **C** higher HbA1c levels after PCI

prognosis ($p < 0.05$). Thus, they are key indicators in assessing prognosis following PCI (Table 3).

Correlation of AG and HbA1c with LV function and inflammatory factors

AG and HbA1c were positively correlated with LVESD, LVEDD, TNF-α, IL-6, and CRP levels and negatively correlated with LVEF levels ($p < 0.05$), showing that high stress hyperglycemia with high HbA1c levels upon admission is a key factor in exacerbating LV injury and inflammatory response (Table 4).

Discussion

PCI can effectively open the infarct-related artery and restore blood flow with a reliable efficacy in patients with myocardial infarction. However, diabetes combined with myocardial infarction often deteriorates the condition, and some patients exhibit poor coronary artery reperfusion, poor recovery of left ventricular function, and a poor prognosis following PCI. Therefore, effective predictors of the prognosis in patients with diabetes mellitus combined with myocardial infarction are crucial in improving prognosis.

Stress hyperglycemia is caused by the dysregulation of the neurohumoral system due to an endogenous or exogenous stress response, wherein the liver overproduces glucose and insulin resistance in response to stress and promotes the secretion of stress hormones, such as glucagon, cortisol, and adrenaline, via the gluconeogenic pathway [11]. This study showed that CRP, TNF-α, and IL-6 levels were higher in patients with high stress hyperglycemia and high HbA1c levels, especially in group B (AG ≥ 120 mg/dL and HbA1c ≥ 6.5%). High stress hyperglycemia with HbA1c levels upon admission exacerbates the inflammatory response. A plausible explanation is that patients with diabetes mellitus combined with myocardial infarction develop an inflammatory response due to myocardial ischemia and insulin resistance, while HbA1c stimulates endothelial cells to produce a variety of cytokines and activate mononuclear macrophages, further aggravating the inflammatory response [12]. The combined effect of glucotoxicity and lipotoxicity accelerates organ and cell death, especially in islet cells, thereby accelerating the development of diabetes [13, 14]. Inflammatory factors, such as CRP and TNF-α, promote gluconeogenesis by inhibiting the insulin receptor signaling

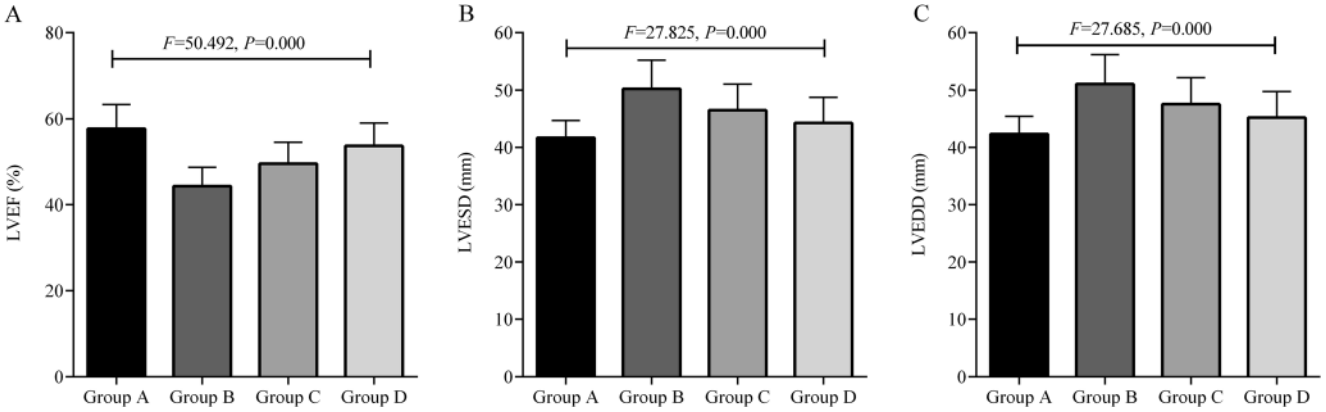

Figure 2 Effect of high stress hyperglycemia and glycosylated hemoglobin on left ventricular function. Note: **A** lower LVEF levels after PCI, **B** lower LVESD levels after PCI, **C** lower LVEDD levels after PCI

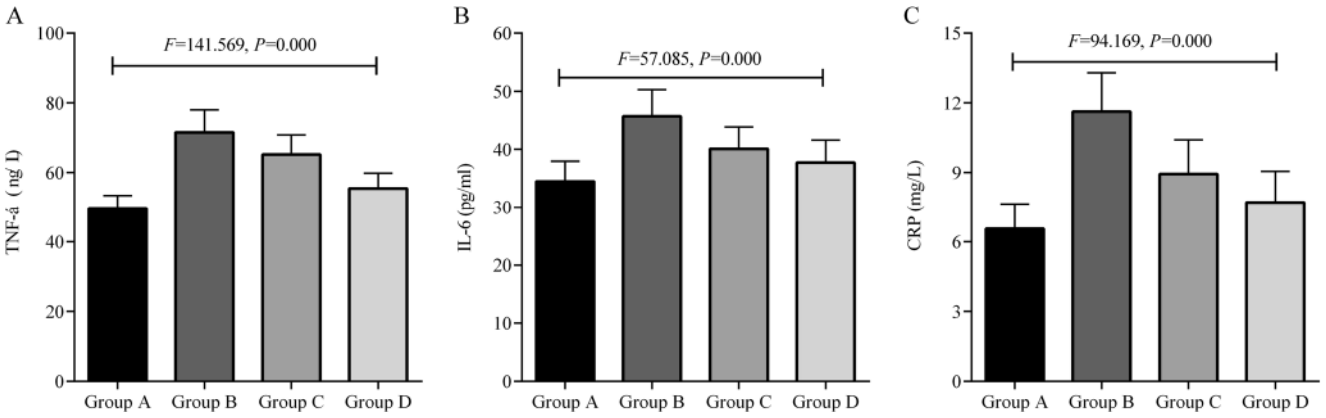

Figure 3 Effect of stress hyperglycemia and glycosylated hemoglobin on inflammatory factor levels. Note: **A** higher levels of TNF-α after PCI, **B** higher IL-6 levels after PCI, **C** higher CRP levels after PCI

transcription system and stimulating glucagon production, such that hyperglycemia and serum levels of inflammatory factors are closely associated with the severity of the condition [15, 16]. After exacerbating the inflammatory response, the persistent hyperglycemia further damages vascular endothelial cells, promotes their dysfunction, inhibits natural anticoagulant substances, stimulates the release of procoagulant factors, and promotes thrombosis [17, 18]. The inflammatory response can also block coronary microcirculation by regulating the expression of cell adhesion molecules, leading to necrosis of the myocardium due to inadequate blood supply [19].

This study demonstrated a higher frequency of endpoint events in group B than in the other three groups, confirming the poorer prognosis of patients with high stress hyperglycemia and high HbA1c levels undergoing PCI. It was reported [20] that high HbA1c levels were positively associated with the mortality rates from cardiovascular disease and that cardiovascular adverse events could be effectively reduced by strict glycemic control (HbA1c < 6.5%), which is similar to the findings of the present study. Hyperglycemia enhances endothelin activity, promotes vasoconstriction, increases the expression of chemokine and adhesion factor, and allows monocytes and lymphocytes to enter the walls of blood vessels and form arterial plaque; glycosylation products accelerate collagen breakdown, which decreases the toughness of the vessel wall, leading to thinning of the fibrous cap and contributing to rupture due to plaque build-up [21]. The pathological manifestations in patients with diabetes mellitus combined with myocardial infarction included abnormal proliferation of new blood vessels or increased vascular permeability and interstitial edema in tissues, leading to thrombosis and atherosclerotic plaque rupture. Therefore, hyperglycemic states can increase the incidence of adverse cardiovascular events [21]. The Canadian Diabetes Association guidelines suggest [22] that an HbA1c level < 6.5% in patients with type 2 diabetes is effective in reducing the risk of cardiovascular mortality.

In addition, this study demonstrated that all indexes of left ventricular function in group B were worse than those in the other three groups, suggesting that patients with high stress hyperglycemia and high HbA1c levels undergoing PCI suffer from the greatest damage to the myocardium. Hyperglycemia has been clinically reported to increase free fatty acids in cardiomyocytes and decrease glycolytic substrates, which trigger a large accumulation of calcium ions, reduce myocardial contractility, and induce arrhythmia [23]. Furthermore, hyperglycemia increases myocardial stiffness and affects ventricular function and myocardial remodeling. Hyperglycemia increases ischemic and hypoxic susceptibility of cardiac myocytes, impairs autonomic regulation, and leads to myocardial structural changes, metabolic disorders, and interstitial fibrosis, causing cardiac diastolic and systolic dysfunction, which impairs left ventricular function.

Table 2 Comparison of endpoint events in four groups (*n* (%))

Indicator	Group A (*n*=38)	Group B (*n*=40)	Group C (*n*=43)	Group D (*n*=39)	χ^2	*p*
All-cause morbidity rate	1 (2.63)	4 (10.00)	2 (4.65)	1 (2.56)		
Non-fatal myocardial infarction	2 (5.26)	3 (7.50)	2 (4.65)	1 (2.56)		
Other MACE events	2 (5.26)	7 (17.50)	2 (4.65)	3 (7.69)		
Total	5 (13.16)	14 (35.00)	6 (13.95)	5 (12.82)	5.318	0.021

Table 3 Regression analysis of AG and HbA1c on prognosis

Indicator	Regression coefficient	Standard error	*Wald*	*p*	*OR*
AG	3.592	1.054	6.518	0.008	0.788
HbA1c	4.716	1.591	5.944	0.005	0.841

Table 4 Correlation of AG, $HbA_{1c}$with LV function and inflammatory factors *r* (*p*)

Indicator	AG		HbA1c	
	r	*p*	*r*	*p*
LVEF	−4.159	<0.05	−4.217	<0.05
LVESD	3.593	<0.05	3.685	<0.05
LVEDD	3.081	<0.05	3.167	<0.05
TNF-α	6.185	<0.05	5.892	<0.05
IL-6	3.123	<0.05	3.645	<0.05
CRP	4.685	<0.05	4.855	<0.05

We observed that AG and HbA1c were positively correlated with LVESD, LVEDD, TNF-α, IL-6, and CRP levels, and negatively correlated with LVEF levels, suggesting that higher blood glucose levels are associated with greater cardiac function impairment and a higher inflammatory response. Therefore, AG and HbA1c levels on admission in patients with diabetes mellitus combined with myocardial infarction should be used as assessment factors for PCI prognosis.

This study has certain limitations. The retrospective nature of this study may lead to a bias in results. In addition, the number of cases studied is small and the study duration is short, which could cause some bias in the data collected. We intend to expand the number of cases and extend the observation period for a more in-depth exploration in our next study.

In summary, we have demonstrated that stress hyperglycemia and high HbA1c in patients with diabetes mellitus combined with myocardial infarction on admission and undergoing PCI are associated with higher FGB and 2hPG levels. This association is responsible for exacerbating ventricular functional impairment and inflammatory response and increasing the risk of endpoint events, and can be a predictor of patient prognosis.

Availability of data and material My manuscript has no associated data.

Code availability Not applicable

Author contribution YYZ wrote draft. YYZ and JW designed the study and reviewed the manuscript. TH and QHY collected the data. QZ and XD performed the statistical analysis. All authors read and approved the final manuscript.

Declarations

Ethics approval This study was approved by the Ethics Committee of Panzhihua Central Hospital.

Consent to participate The research objects and their families were informed and they signed a fully informed consent form.

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

ECW/TBW is increased in type 1 diabetes mellitus patients with diabetic peripheral neuropathy: a retrospective case-control study

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Abstract

Purpose To investigate the result of body impedance analysis (BIA) in type 1 diabetes mellitus patients with diabetic peripheral neuropathy (DPN).

Methods A total of 125 T1DM patients were selected and enrolled into the DPN group (N=30) or the control group (N=95). BIA parameters and clinical characteristics were compared to find possible risk factors. After that, they were screened by binary logistic regression. The receiver operating characteristic (ROC) curve of meaningful index was portrayed, and then, the best cutoff was founded.

Results The DNP group has elder age, longer diabetes duration, higher blood urea nitrogen (BUN) concentration, and lower estimated glomerular filtration rate (eGFR) level. The DNP group has larger odds of other diabetic complications including diabetic peripheral vascular disease (DPVD) and diabetic nephropathy (DN). In BIA parameters, the DPN group had higher ratio of extracellular water (ECW) and total body water (TBW) than the control group (0.3969±0.0097 vs 0.3886±0.0086, p<0.001). Binary logistic regression indicated that increase of ECW/TBW (ECW/TBW≥0.395 vs ECW/TBW<0.395, OR=4.589, 95%CI 1.609~13.091, p=0.004) may be one of risk factors of DPN. In the ROC curve, area under curve (AUC) was 0.752 (95%CI 0.646~0.857) and the best cutoff of ECW/TBW to diagnose DPN was 0.3965.

Conclusion The increase of ECW/TBW may be a new risk factor of DPN and could help doctors predict the risk of DPN in T1DM patients.

Keywords Bioelectrical impedance analysis · Diabetic peripheral neuropathy · Type 1 diabetes mellitus · Body fluid compartment

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune endocrine disease caused by insufficient insulin secretion which results in hyperglycemia and metabolism disorder of fat and protein. The incidence and prevalence of T1DM have been increasing all over the world [1]. Although the latest research shows that although China has the lowest incidence of T1DM in the world (1.01/100,000 per year), the total number of newly diagnosed children in China is the fourth largest in the world [2]. On the other hand, diabetic complications are the main causes of death and disability in patients with diabetes, including cardiovascular disease, stroke, peripheral artery disease, nephropathy, retinopathy, neuropathy, and the reduced ability to fight infection [3]. Diabetic neuropathy is the commonest complication (about 28% in patient of T1DM) [4], causing a heavy public health burden of disease [5]. The most common type of diabetic neuropathy is distal

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symmetric polyneuropathy (approximately 75%), or diabetic peripheral neuropathy (DPN). The clinical presentation of DPN is chronic, symmetrical, length-dependent sensorimotor polyneuropathy followed a "stocking and glove" distribution. The most distal extremities are usually involved first, and then slowly progress proximally, accompanied by tingling, pain, and numbness of skin [6]. Nerve conduction studies are the current golden standard for the diagnosis of DPN [7]. Unfortunately, once DPN has reached a stage at which it is detectable by conventional bedside tools, it might be irreversible at that point [8]. Because treatment typically focuses on pain control, along with modification of risk factors (such as good glycemic control), no treatment is available for reversion or reliable prevention of the disease progression.

The pathophysiology of DPN has not been well illuminated yet, and its etiology is most likely multifactorial [6]. Persistent hyperglycemia leads to an increase in the production of cytosolic and mitochondrial reactive oxygen species (ROS) and reactive nitrogen species (RNS), which cause damage not only to axons of peripheral nerves and its microvasculature, but also to its mitochondrial DNA and nuclear DNA [9]. It is believed that derangements of normal metabolic homeostasis, autoimmunity, and microvascular insufficiency also play an important role in occurrence of DPN [10]. The current research has illustrated that hyperglycemia, metabolic syndrome (obesity), hypertension, hypertriglyceridemia, age, smoking, and particular gene are the risk factors of DPN for T1DM patients [11]. It also reported that the odds of DPN increased with worse renal function (OR 1.96 [1.03–3.74] for estimated glomerular filtration rate levels <30 vs ≥90 mL/min/1.73 m^2) by a population representative study enrolled 5558 T1DM patients from Scotland [12].

Bioelectrical impedance analysis (BIA) is a newly developing examination measuring resistance of human body under alternating voltage of different frequencies. The cell membrane is an insulator at low frequency, extracellular fluid is responsible for the body resistance. While the cell membrane acts as a perfect capacitor at very high frequency, therefore total body resistance reflects the combined of both extracellular and intracellular fluid [13]. Using BIA equations and established procedures, BIA allows determination of fat-free mass, total body water (TBW), extracellular water (ECW), and other relevant indexes. On the basis of theoretical principles, BIA is most appropriately reserved for the assessment of body hydration [14]. Because the equipment is portable and safe, the procedure is simple and noninvasive, and the results are reproducible and rapidly obtained; BIA has become a very prevalent method among hospitalized patients as well as people having health examination in China, which can be used in monitoring of body fluid volumes [15–17], assessment of obesity [18, 19], and status of nutrition [20]. Although quite many studies have been focused on BIA and body composition analyze in type 2 diabetes mellitus (T2DM), few studies have been conducted on type 1 diabetes mellitus. Hence, we carried out this research in order to find out association between BIA parameters and DPN among T1DM patients.

Materials and methods

The current study was a retrospective case-control study which included all adult T1DM patients hospitalized in our hospital who had performed BIA from January 2016 to June 2021. Diagnosis of type 1 diabetes was based upon clinical presentations and positive islet cell autoantibodies. In order to eliminate potential influence of the fluid status and lipid metabolism, patients with dysfunction of other endocrine organs, including pituitary, thyroid, parathyroid, and gonad, were excluded from the study according to blood hormonal levels and symptoms. The following participants were excluded from the study: with heart failure, with cachexia, with hepatitis or liver cirrhosis, with renal failure (serum creatinine>442μmol/L), and pregnancy. Finally, the study population comprised 125 T1DM patients aged 18–73. Mean body mass index of 125 patients was 20.89 (±2.94) kg/m^2. All the patients were on the diabetic diet and did not take extra exercise beside activity of daily life during hospitalization. No patient with diabetic foot ulcers or foot deformities was included in the study. Informed consent from each patient was not required due to the retrospective case-control study design and the use of anonymized data.

Every patient took part in diabetic neuropathy screen in our hospital. Five examinations were included in the screen: ankle jerk, vibration sensation, pressure sensation, temperature sensation, and needling pain sensation. All these examinations were conducted by trained nurses with a vibration perception threshold determinator (Sensiometer A200, Laxons, China). According to the Chinese guideline on diagnosis of diabetic neuropathy of 2021 edition [21], the diagnostic criteria of DPN were as follows: (1) a clear history of diabetes; (2) neuropathy at or after the diagnosis of diabetes; (3) clinical symptoms of neuropathy, such as pain, numbness, and paresthesia, and abnormality of any one of the five examinations; if there are no clinical symptoms, any 2 abnormalities of the 5 tests can be diagnosed; (4) except for neuropathy caused by other causes. According to whether DPN occurred, the patients were divided into the control group (N=95) and the DPN group (N=30).

All data was retrieved from previous hospital records of patients admitted to our hospital. Venous blood was collected after fasting overnight. High-performance liquid chromatography (HPLC) with a hemoglobin A1c analyzer (TOSOH Corporation, Japan) was used to determine glycated hemoglobin (HbA1c). Total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), uric

acid (UA), serum creatinine (SCr), and blood urea nitrogen (BUN) were analyzed using an automatic biochemistry analyzer (Beckman Coulter Analyzer AU58 Series, USA). Estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine concentration using the Xiangya equation [22]. The novel equation provides more accurate GFR estimates in Chinese adults than other formulas.

The values of height and weight were taken with the subjects wearing light clothing and without shoes. The height was determined to the nearest 1 cm and the weight was determined to the nearest 0.1 kg. We use BIA (InBody720 body composition analyzer, InBody, Seoul, Korea) with an established protocol to assess fluid status parameters including ECW and TBW as well as body composition parameters including fat mass, body muscle, and visceral fat area (VFA).

The normality of all characteristics was tested by the P-P plot before performing parametric tests. Normally distributed continuous data are shown as the mean±SD; otherwise, they are expressed as the medians with interquartile ranges. Categorical variables are represented as percentages. To analyze differences between the two groups, variables with a normal distribution were tested by *t*-test, while non-parametric test was used to test skewed ones, and chi-square test to the data of ratio. Fisher's precision probability test was used when any of the four theoretical frequencies is less than five. Parameters with statistical differences between the DPN group and the control group constituted the co-variates and whether complicated with DPN constituted the dependent variable. Binary logistic regression analysis was used to determine which parameters were risk factors of DPN. What's more, the receiver operating characteristic (ROC) curve of meaningful parameter of DPN had been portrayed to access its diagnostic significance. All *p* values were two-tailed, which less than 0.05 were considered statistically significant. SPSS version 22.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Data were collected from 125 Chinese patients including 71 males and 54 females with an age ranging from 18 to 73. Anthropometric and clinical characteristics of the patients were illustrated in Table 1. There was no significant difference between the DNP group and the control group in BIA parameters except ECW/TCW. The DPN group had higher ratio of ECW/TBW than the control group (0.3969±0.0097 vs 0.3886 ±0.0086, $p<0.001$). The DPN group had older age (45.6±15.6 vs 35.8±14.8 years, $p=0.002$) and longer duration of diabetes (10.2±5.2 vs 5.5±6.4 years, $p<0.001$). The DNP group also has larger proportions of diabetic peripheral vascular disease (DPVD) (60.0% vs 24.2%, $p<0.001$) and diabetic nephropathy (DN) (36.7% vs 8.4%, $p=0.001$). Besides, the DPN group has higher BUN (5.7±3.1 vs 4.7±2.2, $p=0.043$) concentration and lower eGFR (94.3±21.0 vs 104.9±19.5, $p=0.012$) than the control group.

According to the explanation of result from the InBody company, a normal ECW/TBW is 0.36 to 0.39. The value of ECW/TBW between 0.39 and 0.40 is determined as mild dropsy, and the value larger than 0.40 is defined as dropsy. ECW/TBW in the DPN group is 0.3969±0.0097, which means that most patients in the DPN group were suffering from mild dropsy.

Age, duration of diabetes, DPVD, DN, ECW/TBW, BUN, and GFR were selected as possible risk factors into binary logistic regression analysis. We chose 0.395 as cutoff value of ECW/TBW because it is slightly less than the average of the DPN patients. The result of the regression is illustrated in Table 2. Longer duration of diabetes (OR=1.099, 95%CI: 1.011~1.196, $p=0.027$), ECW/TBW≥0.395 (OR=4.589, 95%CI: 1.609~13.091, $p=0.004$), DPVD (OR=3.841, 95%CI 1.072 ~13.765, $p=0.039$), and DN (OR=6.182, 95%CI 1.429~26.738, $p=0.015$) may be risk factors of DPN for T1DM patients.

On the other hand, the authors had drawn the ROC curve (Fig. 1) for ECW/TBW in predicting DPN in T1DM patients. The area under curve (AUC) of the ROC curve is 0.752 (95%CI 0.646~0.857), and corresponding cutoff to the maximum of Youden's index (41.9%) is 0.3965, of which the sensitivity is 0.567, and the specificity is 0.853.

Further statistical analysis in this study had indicated that ECW/TBW is relevant to age (Pearson correlation coefficient=0.192, $p=0.032$), sex (male vs female: 0.3889±0.0091 vs 0.3930±0.0097, $p=0.017$), DPVD (0.3936±0.0102 vs 0.3892±0.0089, $p=0.017$), and DN (0.3954±0.0083 vs 0.3898±0.0095, $p=0.019$). To our surprise, the BIA parameter is not correlated to the SCr, BUN, and eGFR.

Discussion

The relationship between ECW/TBW and DPN or other diabetic complications had not been studied before this study. This study shows that ECW/TBW is increased in T1DM patients with DPN, DPVD, or DN. Increased ECW/TBW may be a new risk factor of DPN and could help us diagnose and screen DPN in T1DM patients.

Why is ECW/TBW increased in T1DM patients with DPN? The reason is still unknown. But here are two possible explanations: Firstly, incremental ratio of ECW and TBW could be a result of the course of diabetes. With elder age and longer duration of diabetes, some patients complicated with DPN, DPVD, or DN. These complications usually coexist, because they share similar pathophysiological mechanisms and some risk factors. ECW/TBW of these patients naturally go up as a manifestation of aging, microcirculatory

Table 1 Anthropometric and clinical characteristics

Characteristics	The DPN group	The control group	*p*
N	30	95	
Ages (years)	45.6±15.6	35.8±14.8	0.002**
Duration of diabetes (years)	10.2±5.2	5.5±6.4	<0.001**
Male gender (%)	18 (60.0%)	53 (55.8%)	0.685
Smoking history (%)	9 (30.0%)	26 (27.4%)	0.780
Drinking history (%)	9 (30.0%)	19 (20.0%)	0.252
Hypertension (%)	7 (23.3%)	10 (10.5%)	0.122
DPVD (%)	18 (60.0%)	23 (24.2%)	<0.001**
DN (%)	11 (36.7%)	8 (8.4%)	0.001**
Height (cm)	169.1±9.6	168.8±8.9	0.872
Weight (kg)	59.1±10.0	59.8±10.4	0.727
BMI (kg/m^2)	20.6±2.8	21.0±3.0	0.541
Body fat (kg)	10.6±5.1	12.4±6.1	0.140
Body fat rate	17.4%±8.1%	20.4%±8.1%	0.088
VFA (cm^2)	56.0±24.5	58.1±28.4	0.710
Body muscle (kg)	45.8±8.9	44.6±7.8	0.492
Skeletal muscle (kg)	26.2±5.6	25.9±5.0	0.749
Body protein (kg)	9.4±1.9	9.2±1.6	0.696
Inorganic salt (kg)	3.3±0.57	3.3±0.56	0.475
TBW (L)	35.8±7.0	34.7±6.1	0.385
ECW/TBW	39.69%±0.97%	38.86%±0.86%	<0.001**
FPG (mmol/L)	9.1±7.1	9.9±5.2	0.520
HbA1c (%)	9.7±2.2	10.6±2.6	0.107
TC (mmol/L)	5.0±1.4	5.1±1.4	0.862
TGs (mmol/L)	0.80 (IQR: 0.64–1.07)	0.93 (IQR: 0.64–1.30)	0.260
HDL-c (mmol/L)	1.6±0.5	1.5±0.4	0.254
LDL-c (mmol/L)	2.8±1.1	2.9±1.1	0.587
Uric acid (mmol/L)	286.3±85.8	255.1±85.3	0.099
SCr (μmol/L)	65.5±30.6	57.4±20.8	0.102
BUN (mmol/L)	5.7±3.1	4.7±2.2	0.043*
eGFR	94.3±21.0	104.9±19.5	0.012*
Microalbuminuria (mg/L)	7.5 (IQR: 3.4–223.3)	5.8 (IQR: 3.3–10.8)	0.110

DPN diabetic peripheral neuropathy, *DPVD* diabetic peripheral vascular disease, *DN* diabetic nephropathy, *BMI* body mass index, *VFA* visceral fat area, *TBW* total body water, *ECW* extracellular water, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *TC* total cholesterol, *TGs* triglycerides, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *SCr* serum creatinine, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration. *p<0.05; **p<0.01

Table 2 The result of binary logistic regression analysis of DPN

Variables	*B*	S.E.	Wald	Df	*p*	Exp(*B*) (95%CI)
Age	0.005	0.025	0.047	1	0.828	1.005 (0.958, 1.055)
Duration of diabetes	0.095	0.043	4.862	1	0.027*	1.099 (1.011, 1.196)
DPVD	1.346	0.651	4.270	1	0.039*	3.841 (1.072, 13.765)
DN	1.822	0.747	5.944	1	0.015*	6.182 (1.429, 26.738)
ECW/TBW≥0.395	1.524	0.535	8.115	1	0.004**	4.589 (1.609, 13.091)
BUN	−0.075	0.136	0.307	1	0.579	0.928 (0.711, 1.210)
eGFR	0.004	0.020	0.047	1	0.828	1.004 (0.966, 1.044)
Constant	−3.706	3.009	1.517	1	0.218	0.025

DPN diabetic peripheral neuropathy, *DPVD* diabetic peripheral vascular disease, *DN* diabetic nephropathy, *TBW* total body water, *ECW* extracellular water, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration; *p<0.05; **p<0.01

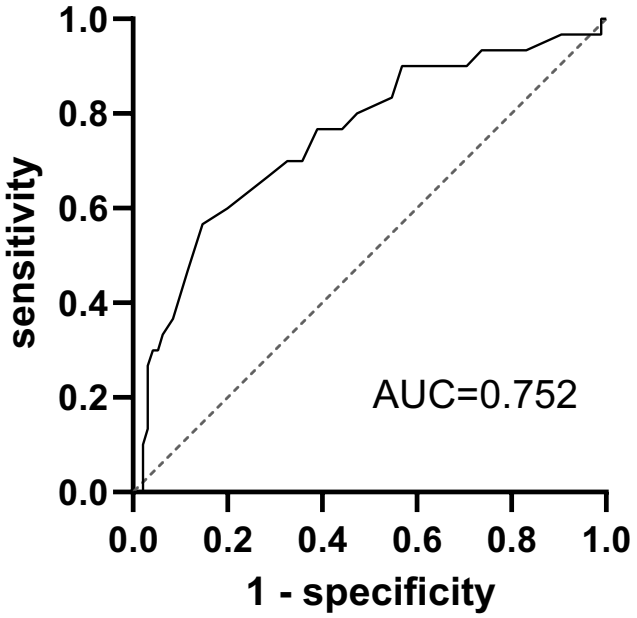

Fig. 1 ROC Curve for ECW/TBW in predicting DPN in T1DM patients. Area under curve=0.752 (95%CI 0.646~0.857) $p<0.001$

disturbance, and renal dysfunction. A cohort study had illustrated that patients with type 2 diabetes and foot insensitivity are at increased risk of eGFR decline [23]. Similarly, DPN patients with T1DM may be in danger of excess extracellular water. Secondly, augmented ECW/TBW could be a reason to DPN. We speculated that higher ratio of ECT/TBW indicates derangements of metabolic homeostasis and microvascular insufficiency, which could damage peripheral nerves. Binary regression shows that the BIA parameter is closely related to DPN, indicating that dropsy may be an independent risk factor to DPN. Further prospective research is needed to make it clear.

Other risk factors of DPN in this research are worth noting, too. Firstly, DPN patients were much more likely to have other diabetes complications. This fact indicates these complications share the same pathophysiology basis of persistent hyperglycemia. Secondly, Chinese T1DM patients generally have low BMI. According to a study which enrolled 356 classic T1DM and 658 latent autoimmune diabetes of adults (LADA), the mean BMI is 21.38±3.47 for classic T1DM and 22.87±3.66 for LADA [24]. So unlike in western countries, obesity may not play an important role in the occurrence of DPN in Chinese T1DM patients. Thirdly, the relationship between DPN and renal insufficiency remains to be seen. It has been reported that in type 2 diabetes patients, lower eGFR is associated with the risk of DPN, even normal or mildly abnormal eGFR may be predictive factors of DPN [25]. In this research, the DPN group has lower eGFR and higher BUN than the control group. But further study is needed to make it out whether mildly impaired kidney function or DN is a risk factor of DPN in T1DM patients.

As to diagnostic value for DPN, BIA can never parallel with nerve conduction studies and other bedside neurological test. It is impossible for BIA to replace them to become the golden standard for DPN, but excess ECW could act as a "red light" to alarm patients and doctors the possibility of diabetic complications.

New questions come with the current research: Whether or not ECW/TBW is increased in T2DM patients with DPN or other diabetic complication? Is the rise of ECW/TBW a risk factor of these complications or just a result of diabetes progression? These problems deserve further research in the future.

Of course, there were a few limitations of this study. First of all, the number of the DNP group is not very much, making the conclusion a little unreliable. Secondly, other situations, such as dapagliflozin [26], dose of insulin, and intake-output number volume, may also affect the outcome of ECW/TBW. But these situations were not taken into consideration in the current research.

In conclusion, this study reveals an interesting phenomenon: The ratio of ECW and TBW is increased in T1DM patients with DPN. This phenomenon has not been reported before. The increase of ECW/TBW may be a new risk factor and a new screen characteristic for DPN in T1DM. It shed light on further research to BIA, dropsy, and diabetic complications.

Declarations The authors declare no competing interests.

Ethics approval This study was approved by the Ethics Committee of Shandong Provincial Hospital affiliated to Shandong University and its protocol was in line with the Declaration of Helsinki (as revised in Brazil in 2013).

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ORIGINAL ARTICLE

Personalized glycemic response led digital therapeutics program improves time in range in a period of 14 days

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Abstract

Background Lifestyle modification is an integral aspect for the management of type 2 diabetes (T2D). However, it is difficult to ensure the accuracy of personalized lifestyle advice. The study aims to analyse the real-world effectiveness of personalized glycemic response based Diabefly-Pro digital therapeutics for better glycemic control.

Methods Data from continuous glucose monitoring (CGM) of 64 participants with T2D was analysed. All participants were provided with modified lifestyle plan based on their personalized glycemic response. The CGM data was analysed for a period of 7 days, before and after the introduction of modified lifestyle plan. Primary outcome of the study was change in time in range (TIR). Secondary outcomes of the study were change in mean blood glucose, time above range (TAR), time below range (TBR) and glucose management indicator (GMI).

Results Significant improvement in glycemic control was observed after the introduction of personalized lifestyle plan. Median reduction in mean blood glucose was from 139.5 (118.3 to 169.3) mg/dL to 122.0 (101.5 to 148.8) mg/dL ($p < 0.0001$). TIR and GMI improved from 70.50 (50.75 to 83.50) % to 75.00 (58.25 to 89.00) % ($p = 0.0001$) and 6.64 (6.13 to 7.35) % to 6.23 (5.74 to 6.86) % ($p < 0.0001$) respectively. TAR reduced significantly from 17.00 (4.25 to 38.0) % to 6.00 (1.25 to 26.0) % ($p < 0.0001$). No significant increase in TBR was observed ($p = 0.198$).

Conclusion Personalized glycemic response-based Diabefly-Pro digital therapeutics program was effective in achieving better glycemic control in people with T2D.

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Keywords Digital therapeutics · Diabetes · Continuous glucose monitoring · Personalized glycemic response

Introduction

Diabetes is one of the fastest growing health challenges with an increasing prevalence rate across the world. The global prevalence of diabetes was estimated as 463 million people which is expected to rise to 578 million by 2030 [1]. India ranks second in the world with 77 million people with diabetes in 2019, which is expected to increase to 101 million by 2030 [1]. The rising prevalence of diabetes has been attributed mainly to increasing cases of type 2 diabetes (accounting for around 90% of total cases) due to ageing, rapid urbanisation and increase in the level of risk factors like obesity, unhealthy diet and physical inactivity [2, 3]. It has been shown that adequate glycemic control among people with diabetes leads to reduction in both macrovascular and microvascular complications [4, 5]. In India, the poor level of glycemic control has been highlighted in many studies [6, 7]. The huge burden of diabetes, lack of access to trained diabetes educators, poor diabetes knowledge in patients, poor communication with healthcare teams due to pre-existing heavy loads at clinics and lack of continuous personalized interventions limits holistic management of diabetes in India [8]. The conventional mode of delivery of lifestyle management lessons using face-to-face interventions are now even more limited after the COVID-19 pandemic [9]. Thus, effective management of diabetes requires virtual patient engagement in addition to clinician's support.

Lifestyle management and behavioral modification is an integral aspect for the effective prevention and management of T2D [10–12]. It includes diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), physical activity, weight loss, smoking cessation counselling, and psychological support [13]. DSMES is aimed at developing the skill and ability of the patients to make informed decisions, problem solving; while the support assists patients to continue the implementation of learned skill and behaviors [14]. MNT is a demanding part of lifestyle management aimed at promoting healthy eating patterns where each individual requires a personalized solution. MNT has been recommended for patients with diabetes and has been shown to improve glycemic control in people with T2D [15, 16].

Last three decades have witnessed rapid development in digital and wireless technologies for the management of diabetes in the field of lifestyle modification, better medical devices (blood glucose meters, continuous glucose monitoring (CGM) devices) [17, 18]. Digital therapeutics have emerged as a new modality for the prevention and management of disease based on evidence-based intervention driven by use of software. Application of digital therapeutics enables large-scale deployment of treatments in a cost-effective manner wherein people can engage with the platform several times a day leading to improved outcomes as compared to conventional treatment [19, 20]. Globally, digital therapeutics technology has shown immense potential to help in the management of diabetes [21, 22]. To our knowledge, there is no personalized glycemic response-based digital therapeutics program currently present in India. The increasing burden of diabetes and relative lack of healthcare resources underline an urgent need for personalized digital therapeutics programs.

The current study is aimed at exploring the real-world effectiveness of Diabefly-Pro digital therapeutics program designed for providing lifestyle, nutritional and behavioral coaching to people with T2D with the use of connected medical device (like CGM) based on their personalized glycemic response for better glycemic control. We analysed the real-world data on glycemic parameters collected from CGM for 14 days. The effectiveness of the program was analysed on the basis of parameters like mean glucose, time in range (TIR), time above range (TAR), time below range (TBR) and glucose management indicator (GMI). The correlation of TIR with diabetes complications has been established in various studies [23, 24].

During the program, a personalized lifestyle plan was created based on the individual glycemic response during the first 7 days of the study while following their usual lifestyle. The variation in glycemic parameters for 7 days, pre and post the introduction of the personalized lifestyle plan was analysed to understand the change in glycemic control. Thus, the study was aimed at the analysis of effectiveness of the personalized lifestyle plan provided to participants based on CGM monitoring using the digital therapeutics platform.

Materials and methods

Study design

The study involved the analysis of de-identified data from 64 participants with T2D using the Diabefly-Pro program (Fitterfly Healthtech Pvt Ltd, Mumbai, India) who continued using the platform for 14 days after program initiation. The participants were recruited based on referrals by clinicians and through social media advertisements. The participants self-declared their T2D status and were contacted through telephone before joining the program wherein the program details were explained to them. The screening was based on the inclusion and exclusion criteria for the study. Eligible candidates who provided written or electronic consent to participate and to provide the de-identified data for research purpose were enrolled in the study. In case consent was not given for use of

data for research, the program participation was provided without any changes in the quality of care. The study was aimed at analysis of de-identified data; no investigational products were used and standard clinical treatment was followed throughout the study.

The inclusion criteria for the study were (1) age ≥ 18 years, (2) owns a smartphone and is willing to utilize the mobile application and (3) has a minimum level of literacy to read and understand in English language. The exclusion criteria of the study included (1) presence of physical, cognitive and psychiatric impairment which can prevent participation in the program; (2) pregnancy; (3) severe complications (end stage chronic kidney failure, chronic liver disease); (4) history of unstable angina pectoris or stroke within the past 6 months; and (5) any recent surgical procedure that causes major physical, cognitive or psychiatric impairment that will prevent participation in program as determined by registered medical practitioner were excluded. Additionally, recent history of gastro-intestinal tract surgery including bariatric surgery which affects the ability to follow dietary regimen led to exclusion of patients.

The primary outcomes of the study were changes in TIR. The secondary outcomes of the study included the change in TAR, TBR, mean glucose and GMI. The study involved the comparison of outcomes for 7 days pre and post the introduction of the personalized lifestyle plan.

Sample size calculation

Minimum sample size for pre- and post-test comparison was calculated using University of California San Francisco online calculator [25]. A sample size of 64 was required to achieve 80% power to detect an estimated standard deviation of the post-over-pre change of 15.88% [26] with an effect size of 0.35 at 5% level of significance using a two-sided Wilcoxon test with Gaussian approximation.

Program

Figure 1 shows the schematic of Diabefly-Pro program which is an evidence-based digital therapeutics program based on personalized glycemic response. The program provides access to the Fitterfly mobile application and helps the participants by creating a personalized lifestyle plan (diet, activity and lifestyle) based on an individual's glycemic characteristics. The digital therapeutics program has been designed to incorporate various features like tools to record and track medical and anthropometric parameters; in-app based extensive Indian food database for tracking calories, macro and micronutrient in meals; digital tracking tools for meals, exercise; in-app access to evidence-based educational and motivational content for diabetes management; support from health coaches (diabetes educators) to manage stress and sleep quality; regular feedback and support from health coaches for building lifelong habits through behavioural modifications. The Diabefly-Pro program also provides access to nutritionists, clinical psychologists and physiotherapists for providing personalized care to people with diabetes.

The Diabefly-Pro program is a 90-day program which consists of three phases; the first phase is the observation phase which involves CGM monitoring based on normal lifestyle (daily meals, activity, sleep quality and stress) of participants; the second phase is the intervention phase where nutritionist and physiotherapist provide every patient with a diet and exercise plan respectively based on their personalized glycemic response data collected from CGM monitoring. Feedback regarding stress management and sleep quality is also provided. The participants are instructed to follow the modified diet and exercise plan and are monitored again for next 7 days using CGM monitoring; the third phase of the program aimed at sustaining the lifestyle modification introduced during the second phase of the program while including regular feedback and support from health coaches to build lifelong lifestyle change for better management of diabetes.

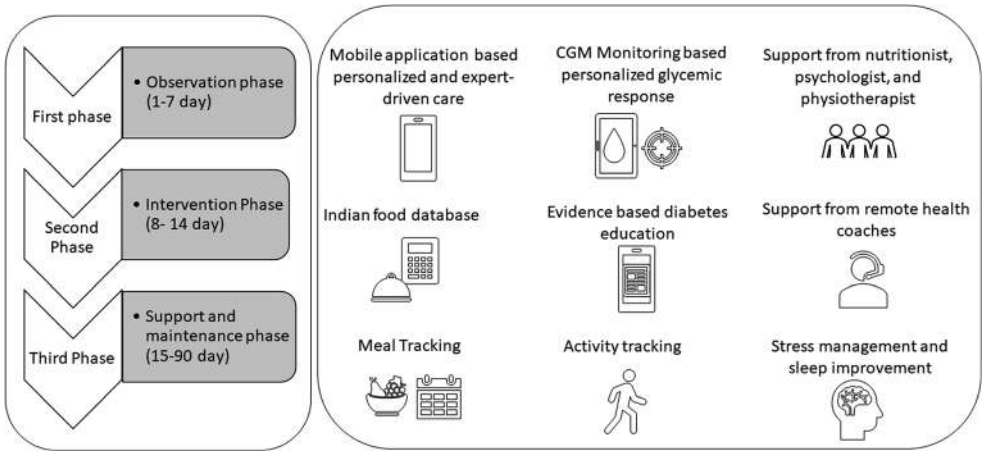

Fig. 1 Schematic of Diabefly-Pro digital therapeutics program

The compliance to the program was ensured through regular video and telephonic calls by remote health coaches every 15 days, providing planned education material containing motivational content for diabetes self-management via mobile application and charging a payment fee for program participation.

Data collection

All the participants enrolled in the program received a link to download the Fitterfly mobile application from both android and ios playstore. A trained program staff performed the application of CGM sensor (FreeStyle Libre Pro, Abbott Diabetes Care) during home visit. The platform used for downloading and collection of the CGM data was FreeStyle Libre Pro Software (Abbott Diabetes care). The study was conducted for 14 days wherein in the initial 7 days the participants followed their normal lifestyle and the CGM data was collected. The data from the CGM sensor was collected at home by trained personnel. The participants also maintained their food and physical activity diary with time stamps in the Fitterfly app. The initial 7 days CGM data was analysed to understand the personalized glycemic response of individuals. After the completion of initial 7 days on the program, the participants were explained their glycemic response to various meals and physical activities. The nutritionist and physiotherapist created a personalized meal and exercise plan for participants based on their initial 7 days. The participants were instructed to follow the recommended personalized lifestyle plan for the next 7 days of the study. The CGM data for the next 7 days was collected again and analysed to understand the effectiveness of the intervention. During the entire duration of 14 days, the participants had access to the Fitterfly mobile application for creating daily log of food diary, physical activity, medication, water intake, sleep and various anthropometric (weight, height, BMI) and clinical parameters (fasting blood sugar, HbA1c). The educational content was also made available to improve the problem-solving ability and to understand the self-care activities for people with diabetes.

Baseline demographic data was provided by participants using the mobile application. The data from CGM included metrics like TIR, TAR, TBR and mean glucose levels. GMI was used as an estimate of glycated hemoglobin level, as described by Bergenstal et al. 2018 [27]. Mean glucose level (CGM) was used for calculation of GMI.

Statistical analysis

The statistical analysis was performed using R software (Version 4.0.3; The R Foundation). Categorical data was represented as number (%); continuous data was expressed as mean (standard deviation (SD)) or median (interquartile range (IQR)) as appropriate for the data distribution. Normality of data was tested using the Shapiro-Wilk test. The comparison of glycemic control parameters pre and post the introduction of personalized lifestyle plan was evaluated using Wilcoxon signed-rank test. $p \leq 0.05$ was considered statistically significant. The variation in TIR among groups with different modalities of management including only lifestyle modification (no pharmacotherapy), oral hypoglycemic agents (OHAs), insulin and combination of OHAs and insulin were compared using one-way analysis of variance. The correlation between change in TIR with the various parameters at the time of enrolment like age, duration of diabetes, weight and BMI was studied using Pearson test for parametric data and Spearman test for non-parametric data.

Results

Table 1 shows the baseline characteristics of 64 participants with T2D enrolled in the study. Overall, the participants consisted of 35.93% (23/64) females; the mean age of the participants was 51.08 ± 11.84 years with an average duration of diabetes of 9.67 ± 8.9 years. The mean weight and BMI of the participants were 72.75 ± 12.36 kg and 26.38 ± 4.0 kg/m^2 respectively. The medication details of participants showed 10.94% (7/64) of participants were using insulin, 37.50% (24/64) used oral hypoglycemic agents (OHAs) and 32.81% (21/64) were using both insulin and OHAs and 18.75% (12/64) did not use any pharmacotherapy (only lifestyle modification). Further, 56.25% (36/64) of the participants were on biguanide, 45.31% (29/64) were on sulfonylurea, 28.13% (18/64) were on dipeptidyl peptidase (DPP)-4 inhibitors, 23.44% (15/64) were on Sodium-glucose cotransporter-2 (SGLT2) inhibitors, 14.06% (9/64) were on alpha-glucosidase inhibitors, 10.94% (7/64) were on thiazolidinediones and 4.68% (3/64) were on other OHAs or non-specified medications. Then, 62.5% (40/64) of patients had comorbidity other than diabetes.

Table 2 shows the changes in glycemic control metrics pre and post the intervention of personalized lifestyle modification plan. The mean glucose in participants reduced significantly from 139.50 (118.30 to 169.30) mg/dL to 122.0 (101.50 to 148.80) mg/dL ($p < 0.0001$). There was a significant improvement in the TIR from 70.50 (50.75 to 83.50) % to 75.00 (58.25 to 89.00) % ($p = 0.0001$). The TAR significantly reduced from 17.00 (4.25 to 38.0) % to 6.00 (1.25 to 26.0) % ($p < 0.0001$). The TBR did not change significantly pre and post the intervention ($p = 0.198$). GMI has been used as an

Table 1 Baseline characteristics of participants

Parameters	Participants (*n*=64)
Gender (Female), *n* (%)	23 (35.93%)
Age, years	51.08 (11.84)
Duration of diabetes, years	9.67 (8.90)
BMI, kg/m^2	26.38 (4.0)
Weight, kg	72.75 (12.36)
Insulin, *n* (%)	7 (10.94)
OHA, *n* (%)	24 (37.50)
Insulin and OHA, *n* (%)	21 (32.81)
Biguanide, *n* (%)	36 (56.25)
Sulfonylurea, *n* (%)	29 (45.31)
Dipeptidyl peptidase (DPP)-4 inhibitors, *n* (%)	18 (28.13)
Sodium glucose Cotransporter- 2 (SGLT2) inhibitors, *n* (%)	15 (23.44)
alpha-glucosidase inhibitors, *n* (%)	9 (14.06)
Thiazolidinediones, *n* (%)	7 (10.94)
Other/ Non specified medication, *n* (%)	3 (4.69)
Comorbid conditions present, *n* (%)	40 (62.50)

approximate measure of lab HbA1c value. GMI improved significantly from 6.64 (6.13 to 7.35) % to 6.23 (5.74 to 6.86) % ($p < 0.0001$).

Figure 2 shows the mean change in mean blood glucose, TIR, TAR and TBR when compared pre and post the intervention. Mean blood glucose was reduced by 18.78 ± 21. 12 mg/dL. Percentage of time in TIR showed a mean improvement of 6.61 ± 13.44%. Percentage of time in TAR and TBR showed a mean reduction of 6.05 ± 11.54% and 2.07 ± 15.58% respectively. GMI showed a mean reduction of 0.45 ± 0.50%.

No significant variation in the change in TIR was observed among groups with different modality of treatment including only lifestyle modification (no pharmacotherapy), OHAs, insulin and combination of insulin and OHAs ($p = 0.48$). The real-world effectiveness of the lifestyle modification plan as quantified through the significant improvement in TIR showed no significant correlation with factors like age ($p = 0.34$) and other parameters recorded at time of enrolment like weight ($p = 0.89$), BMI ($p = 0.71$) and duration of diabetes ($p = 0.32$).

Discussion

The study was aimed at the analysis of real-world effectiveness of Diabefly-Pro digital therapeutics platform providing support based on personalized glycemic response to people with T2D in India. The study was aimed at the analysis of glycemic response 1-week pre and post the intervention of personalized lifestyle plan based on individualized inputs for nutrition and exercise based on CGM monitoring. The results showed that the intervention of personalized lifestyle plan for 1 week in participants led to significant improvement in their metabolic control which was shown by improvement in mean blood glucose, TIR, TAR and GMI. Then, 85.93% (55/64) participants showed reduction in mean blood glucose 7 days post the intervention. Further, 60.93% (39/64) of the participants showed improvement in TIR by ≥ 5%. Moreover, 39.06% (25/64) and 28.12% (18/ 64) showed improvement in TIR ≥ 10% and ≥ 15% respectively.

Every incremental 5% increase in TIR has been associated with significant clinical benefits in people with T2D [23]. Ten percent reduction in TIR has been shown to increase the

Table 2 Change in glycemic control pre and post the introduction of personalized lifestyle plan

Parameters	1 week Pre-Intervention	1 week Post-Intervention	*p* value
Mean glucose (mg/dL)	139.50 (118.30 to 169.30)	122.0 (101.5 to 148.80)	<0.0001
Time in target (%)	70.50 (50.75 to 83.50)	75.00 (58.25 to 89.00)	0.0001
Time above range (%)	17.00 (4.25 to 38.0)	6.00 (1.25 to 26.0)	<0.0001
Time below range (%)	7.50 (1.0 to 21.0)	6.00 (1.00 to 19.25)	0.198
GMI (%)	6.64 (6.13 to 7.35)	6.23 (5.74 to 6.86)	<0.0001

Data represented as median (IQR)

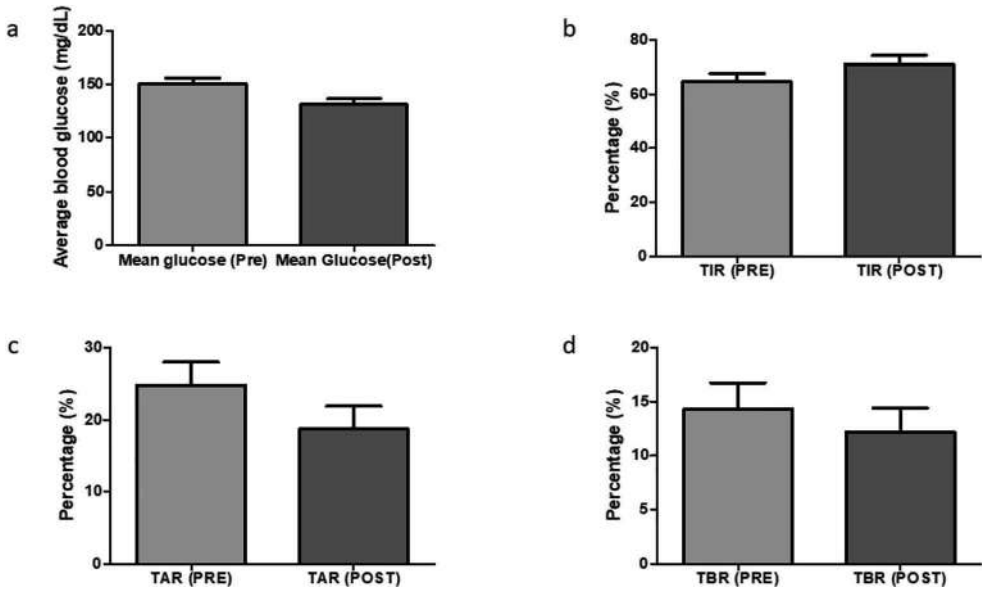

Fig. 2 Mean change in (**a**) mean blood glucose, (**b**) TIR, (**c**) TAR and (**d**) TBR when comparing the values 7 days pre and post the intervention of personalized lifestyle plan

hazard rate for retinopathy progression and microalbuminuria development by 64% and 40% respectively [24]. Time above range decreased significantly suggesting the potential of nutritional modification via intervention leading to reduced glycemic excursion in participants. Postprandial hyperglycemia has been shown to be a direct risk factor for development of cardiovascular disease in people with diabetes [28]. Reduction in mean glucose and GMI showed significant improvement in glucose control in participants using the modified lifestyle intervention for only 1 week.

The current study showed a significant mean change in mean blood glucose, TIR and TAR by 18.78 ± 21, 12 mg/dL, 6.61 ± 13.44%, and 6.05 ± 11.54% respectively. There was no significant increase in TBR post the introduction of lifestyle modification plan. This was similar to results reported for a virtual diabetes clinic for patients with T2D [29]. The study showed a mean increase in TIR by 10.2 ± 20.5%; mean reduction in TAR by 7.2 ± 15.4%; and mean reduction in mean glucose by 14.6 mg/dL at 4 months on the virtual diabetes clinic platform. No change in TBR was observed. TIR has aptly been compared to a "glycemic compass" for evaluation of the health status and to plan for future management strategy in people with diabetes [30]. Digital therapeutic program like Diabefly-Pro can leverage the benefits of TIR to navigate management of T2D towards personalized and expert-driven care based on lifestyle modification.

The change in TIR for groups using different modalities of treatment (which included lifestyle modification (no pharmacotherapy), insulin, OHAs and combination of OHAs and insulin) did not vary significantly. This showed that the pharmacological treatment modality did not affect the effectiveness of the program. Also, the change in TIR did not show significant association with variables like age, duration of diabetes, weight and BMI (at the time of enrolment). Thus, the effectiveness of the program remained uniform irrespective of the variation in all the above parameters.

The study showed the real-world implementation of Diabefly-Pro digital therapeutics program. The study showed significant improvement in glycemic parameters after only 7 days on the personalized lifestyle plan. The 14-day study thus showed significant potential of the program for providing better glycemic control in patients with T2D. The strength of the study includes the remote recruitment, intervention and assessment with low level of missing data. Limitations of the present study include self-selection samples, referral bias and non-randomized design. This approximated the enrolment in real-world commercial programs. The study excluded patients who were not using CGM monitoring. The study population had less participation from women, which might be due to social and economic factors. The study analyzed short-term improvement in glycemic control. Future studies with longer duration, larger sample size and control groups will further confirm the effectiveness of the program.

Conclusion

Results of the study indicated that personalized lifestyle modification based on glycemic data from CGM had a positive impact on the glycemic control of patient with T2D. The study showed the effectiveness of Diabefly-Pro program for providing better glycemic control in patients with T2D. The program showed significant improvement in TIR, TAR, mean glucose within 7 days of introductions of personalized lifestyle plan. Thus, the Diabefly-Pro program is an effective platform for individuals with T2D for achieving clinically significant glycemic control.

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Data availability Due to contractual obligations of Fitterfly Healthtech Pvt. Ltd., the data cannot be shared.

Code availability Fitterfly mobile application is available to download from android and iOS play store.

Declarations

Ethics approval The work involved the secondary analysis of participant data which was deidentified, hence ethical approval was not taken.

Consent to participate Informed consent to participate in the program was obtained from all the study participants.

Consent for publication All study participants provided informed consent to publish the deidentified research data.

Conflict of interest AS is CEO and Co-founder of Fitterfly Healthtech Pvt Ltd. RV, SJ, SM, SB and RR are paid employees at Fitterfly.

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CORRECTION

Correction to: Personalized glycemic response led digital therapeutics program improves time in range in a period of 14 days

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The correct family name of the 9th Author is Samudra.

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ORIGINAL ARTICLE

Insulin antibody as a biomarker to monitor the development of type 2 diabetes in county hospitals in China

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Abstract

Background The significance of insulin antibody (IA) detection in type 2 diabetes mellitus (T2DM) has received scant attention from county hospitals in China. We aimed to introduce exogenous IA positive rate and its relative factors in T2DM treated with insulin in Xiangshan County of Ningbo City, analyzing the immunogenicity of different kinds of insulin.

Methods Patients who were residents from the Danxi community and six towns (Dongchen, Xizhou, Maoyang, Sizhoutou, Juexi, and Qiangtou) in Xiangshan County and diagnosed with T2DM and treated with insulins at Xiangshan Hospital of TCM Medical and Health Group between August 2019 and June 2020 were identified. Those who met the eligibility criteria were included and assigned to the IA-positive or IA-negative group. The immunogenicity of different insulins was compared between the two groups.

Results Among 992 patients, 781 were eligible for IA detection, and 40.2% of them were IA positive. Blood IA was closely associated with fasting and 2-h glucose, insulin, and C peptide levels and higher insulin dosage. Patients receiving basal insulin treatment showed significantly lower blood IA than those treated with mixed human insulin, premixed human insulins, rapid-acting analogs, or a combination of basal and rapid-acting analogs.

Keywords Insulin antibody · Type 2 diabetes mellitus · Primary hospital · Insulin

Introduction

In 2011, 370 million people suffered from diabetes worldwide and 80% of them were from developing countries, according to the estimates released by the International Diabetes Federation. The prevalence has reached 11.6% in China, according to the 2010 report from Chinese Center for Disease Control and Prevention. Patients with type 2 diabetes mellitus (T2DM) roughly account for 90% of all diabetic cases. Insulin is an important means of diabetes treatment. Insulin antibodies (IA) can be developed upon initiation of insulin treatment [1]. Their binding with insulins, forming insulin-antibody complexes which compete with insulins for the binding site of insulin receptors or serve as an insulin pool to reduce insulin activity and irregularly release insulin, ultimately results in hyperinsulinemia and hypoglycemia. Unfortunately, hyperinsulinemia has been proven to be a risk factor of wide glycemic fluctuation [2], increased blood pressure [3], and the occurrence of several tumors [4], Alzheimer's disease [5] and microvascular dysfunction that leads to cardiovascular diseases [6, 7]. Both insulin-antibody complexes and exogenous insulin antibodies (IAs) have been shown to involve in the development of lipoatrophy and microangiopathy, except for glycemic control, via altered insulin pharmacokinetics, insulin resistance, and other mechanisms [8].

As for diabetic complications, patients detected exogenous IA positive due to intake of sulfhydryl-containing agents often suffer from insulin autoimmune syndrome (IAS), which is characterized by spontaneous hypoglycemia and endogenous hyperinsulinemia with a high titer of anti-insulin antibodies. For T2DM patients with insulin therapy, IAs may cause high glucose fluctuation and

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exogenous hyperinsulinemia, which is called exogenous insulin-related insulin autoimmune syndrome (EIAS). IAs preclude the possibility of glucose control and act as a barrier to avoid related complications.

Exogenous IAs have a non-negligible impact on T2DM in China. Dong et al. reported a relatively high ratio of 220/742 exogenous IA-positive patients in Shandong Province [9]. However, the only two studies of exogenous IAs in China were both conducted in urban tertiary 3A hospitals. Any study that provides data for IA-associated measurements of rural patients is urgently needed, who have known risks of treatment incompliance. Therefore, the goal of this study is twofolded: to detect blood IA levels in rural T2DM patients, to explore relationships of exogenous IAs with clinical characteristics of patients and insulin usage in this patient group.

Methods

Subjects and designs

Between August 2019 and June 2020, patients who were residents from the Danxi community and six towns (Dongchen, Xizhou, Maoyang, Sizhoutou, Juexi, and Qiangtou) in Xiangshan County Zhejiang Province and diagnosed with T2DM and treated with insulins at Xiangshan Hospital of TCM Medical and Health Group were selected. Patients diagnosed with T2DM and receiving insulin therapy for at least 2 weeks were included. But they were excluded if they had (1) IAS at or before diagnosis; (2) a history of treatment with sulfhydryl-containing agents in the past 6 months; (3) moderate-to-severe liver or renal dysfunction with alanine aminotransferase (ALT) or glutamic oxalacetic transaminase (AST) > 100 U/L, or estimated glomerular filtration rate (eGFR)< 45mL/(min*1.73m^2); (4) myocardial infarction, cerebral infarction, trauma, operation, and stress state occurred in the past 6 months; (5) acute complications; and (6) types of insulin changed in recent 2 years. The study protocol was approved by the ethical committee of Xiangshan Hospital of TCM Medical and Health Group (p2019-[k]-10).

All subjects were asked to undergo the 75-g oral glucose tolerance test (OGTT) after 10–12 h of fasting. No insulin injection or oral antidiabetic agents (OADs) were administered the night before and on the morning of the test and after the test, with a continuation of insulins. Blood samples were collected during the fasting glucose test and OGTT. We assessed fasting and 2-h post-OGTT glucose, insulin, and C-peptide levels. Fasting blood IA, glutamic acid decarboxylase antibody (GADA), islet cell antibody (ICA), and glycated hemoglobin (HbA1c) levels were quantitated.

Biochemical assays

Serum insulin and C-peptide were determined by immunoelectrochemiluminescence (Roche Diagnostics GmbH, Mannheim, Roche E601, Germany), and hexokinase method was performed to quantitate fasting and 2-h blood glucose levels (Meikang biology, Beckman AU5800, China). We employed high-performance liquid chromatography (Huizhong, Medicine, MQ-2000PT, China) to detect HbA1c. Serum IA was tested with radioimmunoassay (North Institute, Gamma counter sn-6105, China), while ICA and GADA were detected by indirect immunofluorescence assay (Euroimmun, fluorescence microscope EURostarIII, China).

Statistical analysis

Continuous variables were expressed as mean ± standard error of the mean (SEM). Differences between IA-positive and IA-negative groups were compared with the Student *t*-test if data were normally distributed. The chi-square test was applied for categorical variables. All statistical analyses were performed using SPSS24.0 (SPSS, Palo Alto, CA, USA) and Graphpad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). The significance level was set at $p < 0.05$.

Results

IA expression was associated with clinicopathological characteristics

Initially, 992 residents from Xiangshan diagnosed with T2DM were identified. Among others, 211 not fulfilling the eligibility criteria were ruled out, and 781 subjects (78.73%; mean age 61.69 ±11.27 years, range 25–88 years, male-to-female ratio 1.07:1) were enrolled in this study. Among the 781 cases, 40.2% (314 of 781cases) were detected of IA positive. All patients were categorized into the IA-positive (IA+) or IA-negative (IA−) group; IA+ patients showed significant increases in fasting and 2-h blood glucose (FBG, 2hBG; both p=0.000), C peptide (p=0.041 and 0.032), insulin (both p=0.000), and insulin/C peptide ratio (both p=0.000), daily insulin dosage (p=0.000), homeostatic model assessment of insulin resistance (HOMA-IR, p=0.000), and body mass index (BMI, p=0.000) compared to IA− patients (Table 1). There were no pronounced correlations of IA with age, gender, duration of diabetes, duration of insulin treatment, and blood

Table 1 Correlation between IA expression and clinicopathological characteristics of T2DM patients (n=781)

Characteristics	IA+	IA−	*T/Z*	*p*
Number	314	467	-	-
Percentage (%)	40.2	59.8	-	-
Gender (M/F)	174/140	230/237	-	0.091
Age (year)	61.02±10.85	62.14±11.54	−1.364	0.173
Duration of diabetes (year)	9.68±6.75	9.97±7.17	−0.572	0.568
Duration of insulin treatment (year)	4.22±4.26	4.65±4.72	−1.320	0.187
HbA1c (%)	8.29±1.92	8.89±5.85	−1.765	0.078
FBG (mmol/L)	8.38±3.11	9.98±3.58	−6.465	0.000
2HBG (mmol/L)	16.07±5.69	17.93±5.61	−4.514	0.000
C peptide 0 min (nmol/L)	0.69±0.60	0.61±0.40	2.050	0.041
C peptide 120 min (nmol/L)	1.73±1.44	1.53±1.00	2.303	0.032
Insulin 0 min (μIU/ml)	66.52±94.47	10.89±7.33	10.413	0.000
Insulin 120 min (μIU/ml)	129.63±136.99	35.74±31.11	11.938	0.000
insulin/C peptide 0 min	117.18±140.08	23.94±38.59	11.505	0.000
insulin/C peptide (120min)	99.57±156.62	25.89±22.54	8.279	0.000
BMI (kg/m^2)	25.27±3.34	24.38±3.42	3.634	0.000
Daily dosage of insulin (U)	36.57±17.70	30.69±13.70	5.216	0.000
HOMA-IR	25.37±43.81	4.75±3.78	8.318	0.000

The normally distributed date was tested by *t*-test, and measurement data were expressed as mean ± standard deviation. The enumeration data were analyzed by chi-square

HbA1c (all $p > 0.05$, Table 1). Therefore, IA was associated with daily insulin dosage instead of treatment sessions, suggesting that higher insulin dosage may be associated with IA in T2DM.

Serum IA decreases with age

We performed the Nonlin fit of Saturation Binding Data analysis to assess the relationship of serum IA with age in T2DM patients. The results showed that the proportion of IA+ patients decreased by 0.3344 per year of age (Fig. 1).

Insulin regimens associated with IA elevation

Subsequently, proportions of IA+ patients were compared between those treated with different insulin analogs to identify regimens associated with IA elevation. Intriguingly, only 18.1% (19/105) of patients treated with long-acting basal insulin analogs (detemir and glargine) were IA+, significantly lower than the percentages of patients receiving premixed human insulins (novolin and humulin), of 43.1% (197/458), and those receiving premixed rapid-acting analogs (aspart and lispro) and a combination of basal and rapid-acting analogs, of 45.86% (72/157) and 42.62% (26/61), respectively (p<0.05, Fig. 2). No significant differences in the proportion of IA+ patients were found among premixed human insulin group, premixed insulin analogue group, and a combination of basal and rapid-acting analog group (p>0.05). All these indicate that the long-acting basal insulins are less likely to develop IAs.

Discussion

IAs are immunoglobulin, antibodies against insulin, of which IgG-class IAs are most common, followed by IgM-, IgA-, and IgD-class IAs. Insulin often binds to plasma proteins to form multimers. Insulins are primarily targeted by specific antibodies, with binding capacity reaching up to 10,000μU/ml. Once supersaturated insulin is formed, one molecule of IA will antibody can bind to two molecules of insulin, forming an Ab1Ag2 complex (molecular weight 162,000). Specifically, IA-insulin binding can form Ab1Ag2 complexes when a low amount of blood IAs are present or form Ab2Ag1 complexes (molecular weight 306,000) when there are excessive IAs, or constitutes (AbAg)n immune macromolecular complexes when the amounts of insulin and IAs are comparable. However, Ab1Ag2 complexes are unstable, cannot be cleared by the reticuloendothelial system, completely contrary to (AbAg)n complexes [10]. Insulin-receiving individuals with high IA levels and recurrent hypoglycemia had a higher dissociation constant for insulin; furthermore, this study reported that IA characteristics were among the causative factors in hypoglycemic episodes [11]. Therefore, monitoring IA

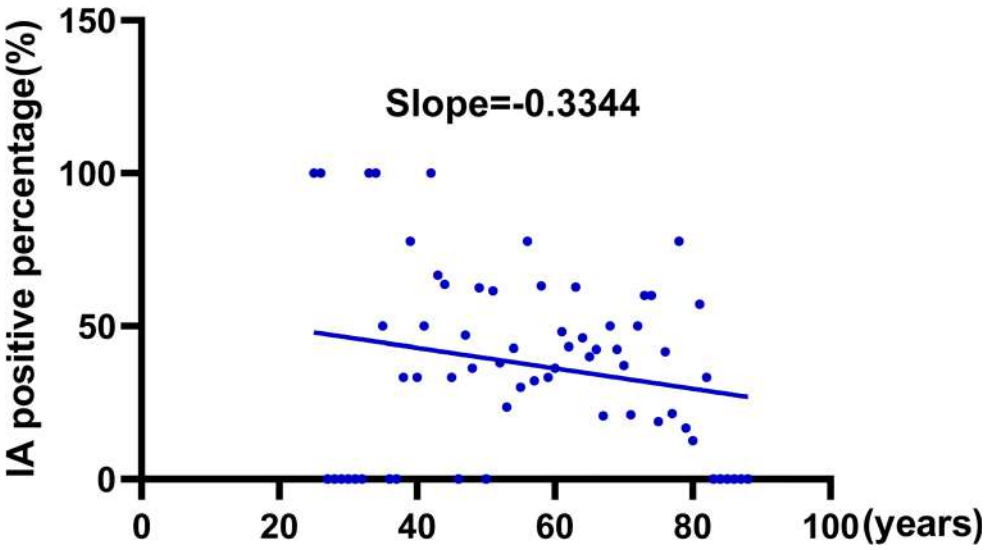

Fig. 1 Serum IA decreases with age

expression monitoring and follow-up treatments of potential complications are particularly important.

In 1960, Harwood first reported the presence of IAs in patients receiving exogenous insulin therapy [12]. As we mentioned above, IA+ patients are more likely to develop hyperinsulinemia more often than IA− patients without IA expression. Due to the mitotic effect of insulin, hyperinsulinemia can promote cell proliferation in vascular wall cells, resulting in thickening of the vascular wall and local deposition of cholesterol. Therefore, hyperinsulinemia has a strong correlation with cardio-cerebrovascular diseases. In addition, IA+ immune macromolecular complexes can cause vascular damage and contribute to diabetic complications.

In this study, blood IAs were detectable in 40.2% (314/781) of all patients, very close to 44% reported by Fineberg et al. [13] in an Indiana population, but much higher than the percentage achieved in an urban Chinese population [9]. This difference can be explained by several reasons. Physicians in county hospitals lack knowledge of the clinical significance of blood IA in T2DM. Glucose control among IA+ patients is unsatisfactory due to glucose fluctuation without regular glucose tests. Furthermore, patients in rural areas often have higher risks of poor compliance with tests or loss to follow-up.

We found that FBG and 2hBG levels significantly decreased and 0' and 120' serum insulin and insulin/C peptide ratio markedly increased in the IA+ versus IA− groups. It can be explained by the biological characteristics of IA [1, 14]. IA accumulation or IA+ complexes in blood have been shown to have a robust ability to bind to a vast array of endogenous and exogenous insulin. Insulin can only be slowly dissociated from the complexes slowly in the absence of exogenous insulins and perform pharmacological actions later. This phenomenon is called a reservoir-like effect [14], which contributes to lower concentrations of FBG and 2HBG in T2DM patients

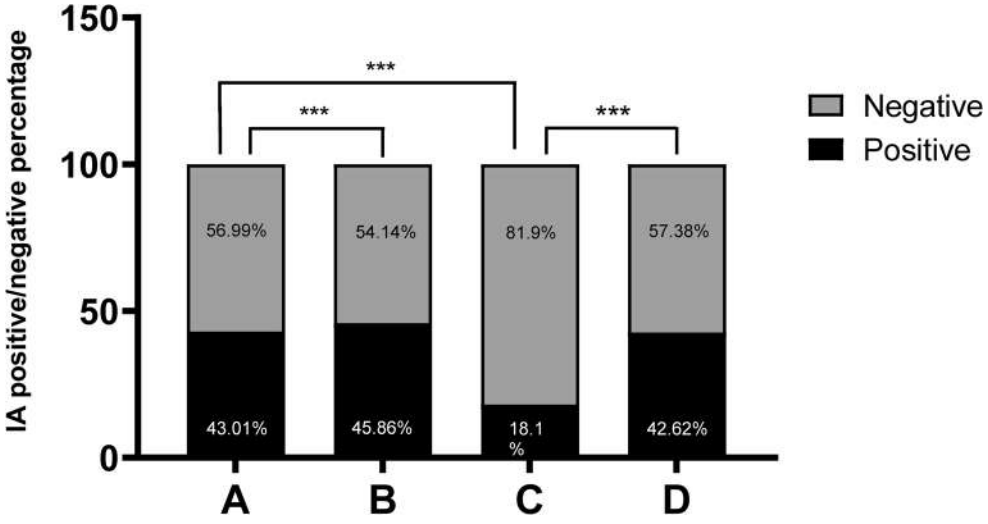

Fig. 2 Proportions of IA+ patients compared between those treated with different insulin analogs

(Table 1). Although IA+ patients exhibited lower FPG and 2hPG levels and greater glucose fluctuation than IA− patients, both of which could not be discriminated by HbA1c.

Previous studies have ascertained that chronic hyperinsulinemia can lead to the decrease of insulin sensitivity [15]. It is reasonable to speculate that hyperinsulinemia in T2DM patients with IA will lead to an inadequate response to insulins, stimulating endogenous insulin production, as manifested by elevated serum C-peptide.

Overweight or obesity may trigger specific and nonspecific autoimmunity [16]. Therefore, BMI may be positively correlated with IA levels. Consistently, we found that BMI in the IA+ group was indeed than that in the IA− group.

Rajan et al. reported that chronic hyperinsulinemia could reduce insulin sensitivity in T2DM patients [16], which required increased insulin dosage. Furthermore, the binding of IA binds to free insulin may reduce the amount of functional insulin in blood, resulting in increased insulin requirement. When insulin combines with IAs with different ratios, insulin-IA complexes of different sizes and molecular weights may exert different biological effects. Their macromolecular complexes can stimulate downstream signaling cascades upon extensive insulin-IA binding. Therefore, blood IAs are more associated with insulin dosage than insulin treatment duration.

In this study, the proportion of IA+ patients among all T2DM patients was comparable between those receiving premixed human insulins and rapid-acting analogs, consistent with the findings reported by Home et al. [17] that there was similar immunogenicity between the two patient groups. As insulin stimulates IA production, patients treated with premixed human insulins group and rapid-acting analogs exhibited significantly higher proportions of IA+ patients than those receiving basal insulin support. The underlying mechanisms can be persistent low serum insulin levels induced by long-acting insulin analogs (insulin multimers) under the skin and weak antigenicity induced by the modified allergenic amino acid B30 in long-acting insulin analogs. Patients receiving a combination of basal and rapid-acting insulin analogs also revealed a higher proportion of IA+ cases than those treated with basal insulin therapy. This may be due to various immune responses triggered by types of insulin analogs [18] and increased risk of IA development by repeated insulin injections [19]. However, mechanisms responsible for a high percentage of IA+ patients among the three insulin regimens have not yet been fully explored.

As for physicians in county hospitals, personalized therapeutic decision-making in T2DM patients to reduce the rate of IA+ patients is feasible to improve blood glucose management and the use of insulin analogs. Thus, diabetic complications can be prevented or delayed to circumvent irreversible organ damage to ameliorate the prognosis and life quality in T2DM patients.

Limitations

The limitations are apparent due to the nature of a single center sampling survey in some villages and towns of county hospitals in China. This cannot represent the specific situation of rural medical care in China, let alone the overall situation in China. These problems can be resolved in multicenter studies in China in the future.

Conclusion

Blood IA is associated with hyperinsulinemia and daily insulin dosage in T2DM. IA+ T2DM patients are more likely to have significant blood glucose fluctuations and hypoglycemia after insulin injections, which can be resolved by adjusting the treatment plan. Special attention must be placed on rural residents as the proportion of IA+ patients from Xiangshan County is much higher than that reported in previous studies, conducted in urban populations.

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Declarations

We the undersigned declare that this manuscript entitled "Analysis of the status of insulin antibody positive rate in T2DM patients in county hospitals in China" is original, has not been published before, and is not currently being considered for publication elsewhere.

We would like to draw the attention of the Editor to the following publications of one or more of us that refer to aspects of the manuscript presently being submitted. Where relevant copies of such publications are attached.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the corresponding author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs.

Ethical Approval The study protocol was approved by the ethical committee of Xiangshan Hospital of TCM Medical and Health Group (p2019-[k]-10).

Conflict of Interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Diabetic retinopathy: long-term follow-up of Ecuadorian patients with type 2 diabetes in primary care

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Abstract

Objectives The aim of this study is to evaluate the prevalence, associated factors, and time for diabetic retinopathy (DR) development in Ecuadorian patients with type 2 diabetes (DM2) followed for 10 years.

Methods A retrospective cohort study between 2007 and 2017 included 487 patients with DM2 who had at least one dilated fundus eye examination in Diabetes Center in a primary-health-care level followed up for ten years. Data was collected from clinical records. Sociodemographic and laboratory variables were analysed, determining their association (mean difference and bivariate logistic regression) with DR. Survival time was calculated through life tables and Kaplan-Meier analysis.

Results The prevalence of DR was 19.95% during the 10-year follow-up period. The median time for developing DR was 28.53 (95% CI: 26.89–27.05), showing that 50% of patients have the risk (HR: 4.57) to develop DR in the third decade of DM disease diagnosis. The significant risk factors for progression of DR were duration of DM2, high glycosylated hemoglobin level > 7% (HbA1c Expβ: 1.709, 95% CI: 1.00–2.89), systemic hypertension (HNT Expβ: 2.348 Expβ: 2.348 95% CI: 1.17–4.70%) 95% CI: 1.17–4.70%), low glomerular filtration rate (Expβ: 1.805, GFR, < 60 ml/min/sc1.73) (95% CI: 1.10–2.94) and albuminuria (Expβ: 2.48 Expβ: 2.48 95% CI: 1.49–4.13).

Conclusions Half of the patients with DM2 treated in a primary level of care will develop DR in the third decade of the disease. There are risk factors related to development of DR, such as low GFR, high HbA1c, albuminuria and HTN. Low GFR, high HbA1c, albuminuria and high blood pressure are related with the presence of retinopathy in diabetes patients.

Keywords Diabetes mellitus · Type 2 · Diabetic retinopathy · Risk factors · Primary level of care

Introduction

Diabetic retinopathy (DR) is a complication present in 30% of the people diagnosed with diabetes, and it is the leading cause of vision loss in working-age adults. In Ecuador, the prevalence of type 2 diabetes mellitus (DM2) is between 3.5 and 8.5% [1], and a local study has reported that the prevalence of DR is 14.8% approximately [2].

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DR is caused by chronic hyperglycemia damaging the retinal microvasculature. The microvascular repercussion at the retinal capillary level (loss of pericytes, basement membrane thickness, and microaneurysms) is the most common consequence of DM2 in the eyes. DR can be classified as non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and diabetic macular edema (DME) [3].

This study aimed to determine the prevalence and associated DR factors, and the survival time for developing DR in an Ecuadorian population with DM2 at the primary level of care.

Materials and methods

This retrospective cohort study included 697 patients with DM2 followed for 10 years from January 2007 to December 2017 registered at the Chimbacalle Primary Care Health Center in Quito, Ecuador. Participants were included if they

were diagnosed with DM2 by the American Diabetes Association (ADA) criteria [4]. Additionally, participants must have medical and laboratory records for a minimum period of 1 year from the baseline, including total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (Tg), glycated hemoglobin (HbA1c), urea, creatinine and albuminuria. Moreover, electrocardiogram [EKG] exam, glomerular filtration rate, calculated with the CKD-EPI formula, and at least one ocular fundus during the study should have been recorded. Participants with type 1 diabetes mellitus diagnosis, under 18 years old, pregnant women, incomplete data in clinical records (n = 48), patients without ocular fundus exam (n = 157) and those previously diagnosed with any chronic ocular disease or blindness were excluded. After exclusion criteria, 487 (69.87%) participants with DM2 remained in the study (Fig. 1).

Retinopathy ascertainment

The ophthalmological examination included visual acuity with and without correction, ocular movements, intraocular pressure, biomicroscopy with a slit lamp, ocular fundus with 78 Dp lenses and indirect ophthalmoscopy. Both retina and vitreous were examined, and DR was diagnosed if signs of capillary microaneurysms, cotton-wool spots, dots or blot retinal hemorrhages, hard exudates, macular edema, venous dilation and intraretinal microvascular abnormalities were found in the ophthalmoscopic exam by a trained ophthalmologist.

Diabetes-related variables

Covariates were selected based on the previously published evidence of their relationship with DR. Covariates included sex, age at DM2 diagnosis, DM duration length in years, smoking status (non-smoker, former or current smoker), hypertension status, body mass index (BMI) calculated as weight divided by height squared in meters (kg/m^2) and categorized using 25 kg/m^2 as cut-off point. Biochemical test information included HbA1c (> 7%), albuminuria (normal/high), TC (> 200 mg/dl) and HDL (> 45 mg/dl for men and > 50 mg/dl for women). Additionally, glomerular filtration rate (GFR) was calculated and categorized (< 60 ml/min/m^2). Systolic and diastolic blood pressure were measured in mmHg by trained personal and arterial hypertension (HTN) was defined according to the Eighth Joint National Committee criteria [5].

Statistical analysis

Participant's characteristics were summarized according to sex. The mean and standard deviation were calculated for quantitative variables, and the relative and absolute frequencies were calculated for qualitative variables.

Furthermore, participants were divided into two groups according to their DR diagnosis status (Retinopathy Yes/No). The statistical differences were calculated using t Student for parametric, and the Mann-Whitney U for non-parametric quantitative variables, and the χ^2 was used for qualitative variables.

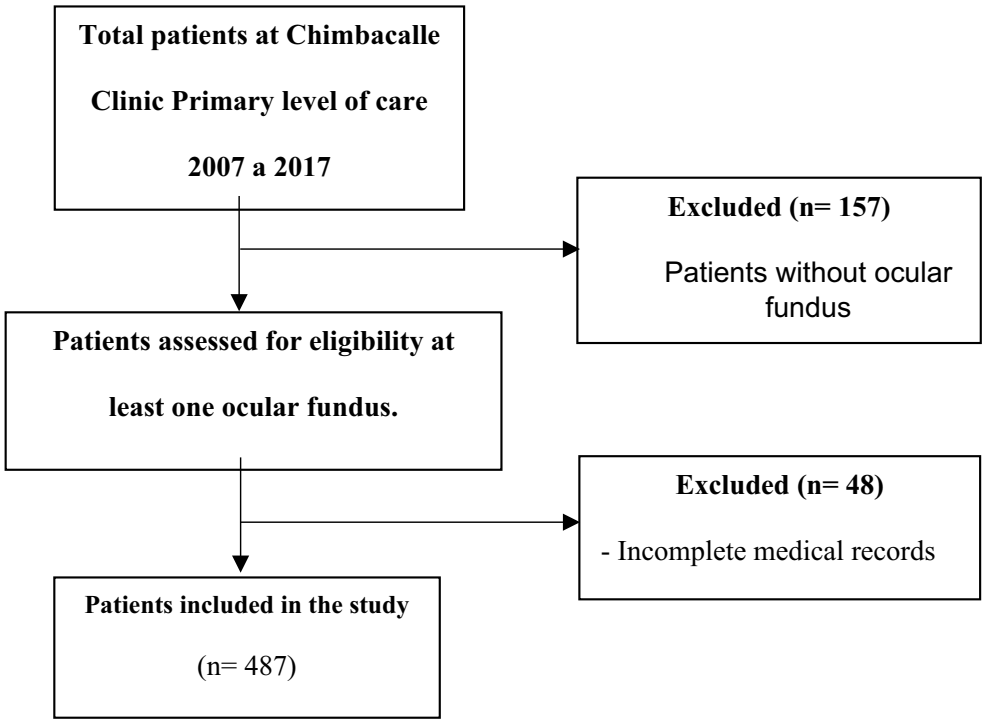

Fig. 1 Flow diagram of eligible participants in the study

For survival analysis, the survival time for the development of DR was the interval between the index time (age at diagnosis of DM2) and the occurrence of the event of interest (diagnosis of DR) or the end of follow-up (December 31, 2017). Life tables were used to estimate the survival time for developing DR.

Binary logistic regression analysis included those variables that were statistically significant in the univariate analysis. All statistical analyses were considered p values < .05 statistically significant and were performed using the statistical software package IBM SPSS Statistics version 23.

Results

Among the 487 patients included in the study, the mean age was 65.82 years, ranging from 31 to 97 years. The mean DM duration was 13.16 years, with 55% (n = 268) of individuals showing a history of DM over 10 years. Additionally, 73.6% (n = 358) had high blood pressure as comorbidity (Table 1).

Overweight was found in 42.5% (n = 207) of the patients, and 38.2% (n = 186) presented some degree of obesity according to their BMI. Regarding glucose levels, 62.4% (n = 304) presented HbA1c higher than 7%. Additionally, concerning lipid profile components, 72.7% (n = 354) individuals showed TC levels under 200 mg/dl, 69.8% (n = 340) had LDL levels less than 100 mg/dl and 51.3% (n = 250) presented inadequate triglyceride values (above 150 mg/dl). On contrast, 83.8% (n = 408) presented HDL values within normal parameters (Table 1).

The behavior of DR was analysed with the sociodemographic characteristics and risk factors. For the year 2017, the prevalence of retinopathy was of 19.95% (n = 96); within the bivariate analysis, we found that the time of disease and time of appearance of DR were significant as well as the presentation of AHT (95% CI: 1.17–4.70%) and control of HbA1c (95% CI: 1.00–2.89), also show a significant association with decreased renal function (Table 2).

Table 1 Characteristics of patients with type 2 diabetes mellitus by sex

	Total n = 487 Mean (DS)	Women n = 391 Mean (DS)	Men n = 96 Media (DS)	p
Age at baseline	65.81 (± 11.64)	65.61 (± 11.41)	66.63 (± 12.56)	0.43
Age at DM diagnosis	52.69 (± 11.51)	52.17 (± 11.11)	54.79 (± 12.83)	0.04*
DM duration (years)	13.16 (± 7.17)	13.35 (± 7.40)	12.43 (± 6.16)	0.26
		n = (%)	n = (%)	p
Normal blood pressure	129 (26.5%)	118 (24.2%)	11 (2.3%)	0.01*
High blood pressure	358 (70.6%)	273 (56.1%)	85 (17.55)	
EKG no changes	357 (73.3%)	294 (60.4%)	63 (12.9%)	0.07
EKG with changes	130 (26.7%)	97 (19.9%)	33 (6.8%)	
Normal albuminuria	378 (77.6%)	323 (66.3%)	55 (11.3%)	0.01*
Increased albuminuria	109 (22.4%)	68 (14.0%)	41 (8.4%)	
HbA1c less than 7%	183 (37.5%)	159 (32.6%)	24 (4.9%)	0.01*
HbA1c higher than 7%	304 (62.4%)	232 (47.6%)	72 (14.8%)	
TC less than 200 mg/dl	354 (72.7%)	292 (60.0%)	62 (12.7%)	0.05*
TC above 200 mg/dl	133 (27. 3%)	99 (20.3%)	34 (7.0%)	
HDL above 50 W 45 M	408 (83.8%)	329 (67.6%)	79 (16.2%)	0.64
HDL less than 50 W 45 M	79 (16.2%)	62 (12.7%)	17 (3.55)	
LDL less than 100 mg/dl	340 (69.8%)	279 (57.3%)	61 (12.5%)	0.17
LDL above 100 ml/dl	145 (29.8%)	111 (22.8%)	34 (7.0%)	
Tg less than 150 mg/dl	237 (48.7%)	189 (38.8%)	48 (9.9%)	0.82
Tg above 150 mg/dl	250 (51.4%)	202 (41.5%)	48 (9.9%)	
Non-smoker	384 (78.8%)	304 (62.4%)	80 (16.4%)	0.26
Former/current smoker	103 (21.2%)	87 (17.9%)	16 (3.3%)	
GFR CKD-EPI > 60 ml/min	279 (57.3%)	242 (49.7%)	37 (7.6%)	0.01*
GFR CKD-EPI < 60 ml/min	208 (42.7%)	149 (30.6%)	59 (12.1%)	

*HDL Cut-point values were 50 mg/dl for women and 45 mg/dl for men

Tg triglycerides, *GFR* glomerular filtration rate, *EKG* electrocardiogram, *TC* total cholesterol, *DM* diabetes mellitus, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *Hb1AC* glycosylated haemoglobin

Among all patients, 96 (19.95%) participants developed DR (n = 96) in the follow-up time. Comparing patients with DR with patients without DR, statistically significant differences were found in age at DM diagnosis, renal function, HBA1c, HDL, blood pressure and categorized TC (Table 2).

In the survival analysis to determine the presence of DR by 10-year period, results showed that 50% of patients would develop DR in the third decade of DM disease (28.56 years) with a 4.57 times increased risk (HR:4.57) (Table 3 and Fig. 2).

Among the variables statistically significant in the univariate analysis, the binary logistic regression results showed an association between DR and renal function TFG_CKD < 60 ml/min (Expβ: 1.805, 95% CI: 1.04–2.949, p value: < .018), HbA1c (Expβ: 1.709, 95% CI: 1.01–2.89, p: .047), HTN (Expβ: 2.348, 95% CI: 1.17–4.71, p value .016), and albuminuria (Expβ: 2.48, 95% CI: 1.495–4.139, p value:.000) (Table 4).

Discussion

Globally, the mean prevalence of DR is 25.2%, with the highest among Hispanic countries which range around 30% [6]. Epidemiological studies showing the prevalence of DR have not been conducted in Ecuador, highlighting the

Table 2 Clinical and metabolic variables according to diabetic retinopathy diagnosis

	No retinopathy (n = 391) mean (DS)	Retinopathy (n = 96) mean (DS)	p
Age until last follow-up (years)	65.38 (11.67)	67.77 (11.36)	0.07
Age at DM diagnosis (years)	53.23 (11.60)	50.52 (10.91)	0.04*
DM duration (years)	12.16 (6.60)	17.25 (7.98)	0.01*
Duration of retinopathy (years)	12.15 (6.58)		
GFR (CKD-EPI ml/min/1.73 m^2)	66.45 (18.99)	52.95 (22.29)	0.01*
< 60 ml/min/1.73 m^2	11.44 (6.79)	15.73 (8.81)	0.01*
< 30 ml/min/1.73 m^2	12.23 (6.90)	17.30 (8.94)	0.01*
HbA1c %	7.51 (1.42)	8.01 (1.36)	0.01*
Total cholesterol (mg/dl)	180.48 (34.06)	187.25 (41.65)	0.09
HDL mg/dl	58.93 (12.96)	62.14 (15.73)	0.03*
LDL mg/dl	88.91 (23.66)	92.57 (30.50)	0.20
Triglycerides (mg/dl)	170.25 (79.29)	159.67 (66.33)	0.23
Sex	n (%)	n (%)	p
Men	75 (15.4%)	22 (4.5%)	0.39
Women	316 (64.9%)	74 (15.2%)	
Blood pressure	n (%)	n (%)	p
High blood pressure	273 (56.1%)	85 (17.5%)	0.01*
Normal blood pressure	118 (24.2%)	11 (2.3%)	
EKG changes	n (%)	n (%)	p
Undisturbed ECG	294 (60,4%)	63 (12%)	0,07
Altered ECG	97 (19,9%)	33 (6,8%)	
CKD-EPI	n (%)	n (%)	p
> 60 ml/min/1.73 m^2	242 (49.7%)	37 (7.6%)	0.01*
< 60 ml/min/1.73 m^2	149 (30.6%)	59 (12.1%)	
Albuminuria	n (%)	n (%)	p
Normal	323 (66.3%)	55 (11.3%)	0.01*
Altered	68 (14.9%)	41 (8.4%)	
GLYCOSYLATED HaEMOGLOBIN	n (%)	n (%)	p
Less than 7%	159 (32.6%)	24 (4.9%)	0.01*
Over 7%	232 (47.6%)	72 (14.8%)	
Total cholesterol	n (%)	n (%)	p
Less than 200 mg/dl	292 (60.0%)	62 (12.7%)	0.05*
over 200 mg/dl	99 (20.3%)	34 (7.0%)	
HDL cholesterol	n (%)	n (%)	p
HDL over 45 AND 50 mg/dl	329 (67.6%)	79 (16.2%)	0.64
HDL less than 45 AND 50 mg/dl	62 (12.7%)	17 (3.5%)	
LDL cholesterol	n (%)	n (%)	p
LDL less than 100 mg/dl	279 (57.5%)	61 (12.6%)	0,17
LDL over 100 mg/dl	111 (22.9%)	34 (7.0%)	
Triglycerides	n (%)	n (%)	p
TG less than 150 mg/dl	189 (38.8%)	48 (9.9%)	0,82
TG over 150 mg/dl	202 (41.5%)	48 (9.9%)	

Tg triglycerides, *GFR* glomerular filtration rate, *EKG* electrocardiogram, *TC* total cholesterol, *DM* diabetes mellitus, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *Hb1AC* glycosylated haemoglobin

*p <0,05 statistically significant

Table 3 Survival curve and survival table

Years	Patients	Censored	Exposed	Retinopathy	% retinopathy	% No retinopathy	% cumulative survival	HR
0 to 10	487	159	407.500	31	7.61	92.39	92.39	0.79
10 to 20	297	188	203.000	42	20.69	79.31	73.28	2.30
20 to 30	67	32	51.000	19	37.25	62.75	45.98	4.57
30 to 40	16	11	10.500	4	38.10	61.90	28.46	4.70

Median survival time is 28.53

importance of this study, focusing on reliable data in a population diagnosed with DM2 at a primary level of care.

This study has shown that the prevalence of DR was 19.5% in a DM2 population, with a mean DM2 duration of 13.16 years. This prevalence is lower than other Latin American countries' reported prevalence of 30% [6]. An analysis of 35 studies conducted in 22,896 people with diabetes on several continents reported a DR global prevalence of 25.2% [6]. In some European countries, the prevalence is slightly higher, ranging from 30 to 40% [7]. According to Varma et al., the prevalence is higher in the Hispanic population [8]. Furthermore, the prevalence in Peru and Chile has been reported at 25.9% and 24.78%, respectively. The authors of these studies have theorized that the reasons may be due to some genetic or obesogenic factors [9, 10].

Factors such as duration of DM, presence of HTN, decrease in GFR, and high values of HbA1c were found significantly associated with DR, as previous evidence has been published.

Therefore, the longer the time of being with DM2, is more likely to develop DR. A study by Zhang et al. conducted in the USA reported that each year of DM2 represents a 6% increase in the likelihood of DR [11].

Furthermore, increased systolic and diastolic blood pressure measurements, regardless of the type of diabetes, were found to increase the risk of DR [12]. Diastolic blood pressure was also an independent predictor of DR in patients with DM2. The United Kingdom Prospective Diabetes Study (UKPDS) showed reduced microvascular complications and visual loss when lowering blood pressure [13, 14].

The prevalence of albuminuria in diabetic patients is 15% to 20%: it is a risk marker for renal and cardiovascular disease and severe ocular morbidity [15]. Evidence has shown that DM2 patients with microalbuminuria were more likely to have retinopathy than those without microalbuminuria [16]. Also, it has been reported that about 45% of diabetic patients with albuminuria have some degree of DR [17].

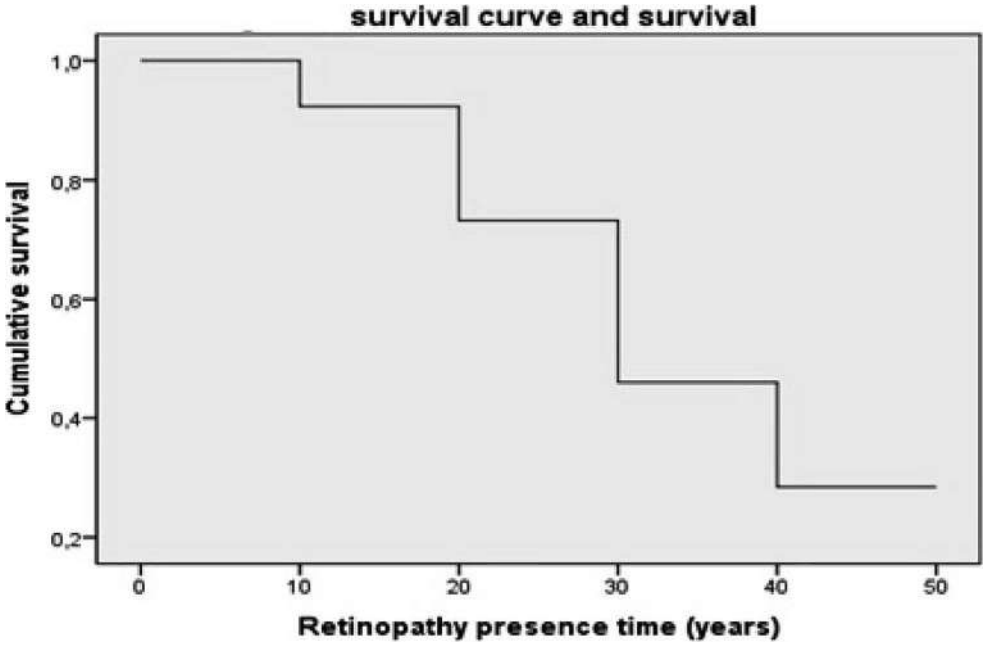

Fig. 2 Survival curve

Table 4 Bimodal multivariate analysis of Diabetic Retinopathy factors

	B	Wald	Sig.	Exp(B)	95% CI for EXP(B)	
					Inferior	Superior
GFR_CKD < 60 ml/min/1.73 m^2	.590	5.554	.018*	1.805	1.104	2.949
Albuminuria > 30	.911	12.306	.000*	2.488	1.495	4.139
HbA1c > 7%**	.536	3.955	.047*	1.709	1.008	2.897
High blood pressure	.853	5.779	.016*	2.348	1.171	4.708

GFR glomerular filtration rate, *Hb1AC* glycosylated haemoglobin

Adequate and continuous control of blood glucose levels in DM2 patients might directly reduce the risk of long-term DR shown in the UKPDS study [12]. In contrast, inadequate glucose control, measured by HbA1c, increases the risk of early DR development, as shown in the ACCORD and ADVANCE studies [18].

To the best of our knowledge, this is the first study conducted in the Ecuadorian DM2 population at the primary level of care and has the potential of becoming a reference retinopathy study in a developing country like Ecuador due to the sociodemographic characteristics of the population. The study also emphasizes the need to have a good and comprehensive care of DM2 to prevent the development of microvascular complications like DR. For this purpose, strict control of the metabolic profile and blood pressure from the moment of diagnosis according to the recommendations of the guidelines is necessary. Furthermore, the authors highlight the importance of having a reliable method to identify patients at the highest risk of DR. Periodic visual controls allow an effective intervention before vision loss occurs.

Among the limitations, we found that it is not a prospective design work of a single cohort, and that the data was gathered in a primary care clinic; therefore, these findings cannot be extrapolated to the general population. However, the results could be applied in patients with a similar context, as the one in the present study. This means a primary care center of the public health system, which focuses on national and international diabetes control recommendations. However, the study has the strength of being a reference in a developing country like Ecuador because of the population and sociodemographic characteristics.

It should be noted that these results could also be attributed mainly to the fact that patients were permanently treated with first-line drugs (ODA) for treatment, including insulin, which in this country are distributed free of charge, thus affordable to all patients.

In conclusion, a low rate of DR is observed due to adequate follow-up and compliance with therapeutic goals in a diabetes clinic. In a primary level of care diabetes clinic, half of its patients will develop DR by the end of the third decade of disease. Important factors to consider when analysing the risk of developing DR include AHT, HbA1c, renal function, age at diagnosis, and time with DM2.

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Declarations

Ethics approval This study was approved by the Institutional Review Board (IRB) of Central University of Ecuador (IRB ref number: 279-CE-UCE-2015). The study adhered to the tenets of the Declaration of Helsinki. All the patients gave their informed consent before the Ophthalmological Control was performed.

Conflict of interests The authors declare no conflict of interest.

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LETTER TO THE EDITOR

Nerve conduction study abnormalities in Indian children with type 1 diabetes

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Nerve conduction study(NCS) is considered the gold standard to detect diabetic sensorimotor peripheral neuropathy (DSPN) in children with type 1 diabetes (T1DM) [1]. NCS abnormalities range from 22 to 97% in children depending on the criterion used, ethnicity, and clinical profile [1]. NCS data in the paediatric population in India is scarce. This single-centre cross-sectional study aimed to explore patterns of DSPN in Indian children/adolescents with T1DM.

This was a single-centre observational cross-sectional study approved by the institutional ethics committee. We recruited T1DM children/adolescents aged 5–18 years without a history of systemic illness and healthy siblings as controls. Abbreviated NCS protocol was performed with Neuropack X1 instrument on sensory sural and motor common peroneal nerves (CPN) of the right lower limb to record amplitudes (Amp) and nerve conduction velocities (NCV) [2], as these two nerves are most sensitive indicators of DSPN [1]. Sample size calculation based on nerve conduction velocity (NCV) data was done to determine the significant difference in NCS parameters between T1DM versus controls. Allowing a margin of error of 2 m/sec on either side of the mean [3] and power of 90%, type 1 error of 5%, the calculated sample size was required to be 25 in each group [4].

Fifty-one T1DM subjects (19 males) and 50 age and gender-matched healthy children (21 males) were recruited. NCS parameters of 50 healthy children (mean ± SD) were sural nerve (amplitude (21.4 ± 5.7 μV), sural nerve conduction velocity (50.8 ± 3.4 m/s)), common peroneal nerve (amplitude (6.0 ± 2.4 mV), CPN-nerve conduction velocity (52.2 ± 4.6 m/s)). Abnormal nerve conduction values were taken as values below 2.5 SD of normal, and these cut-off values were applied to the T1DM cohort to identify children with subclinical neuropathy.

Children with T1DM (age 12.8 ± 3 years, T1DM duration 6.03 ± 2.9 years, HbA1c 9 ± 1.5%) had no or minimal evidence of clinical neuropathy as per Toronto clinical neuropathy score. The most common nerve conduction abnormality in T1DM children was in sural nerve conduction velocity ($n = 15$, 29.4%) followed by sural-amplitude ($n = 7$, 13.7%), peroneal nerve conduction velocity ($n = 6$, 11.7%). Patterns of involvement were pure sensory ($n = 12$), sensorimotor ($n = 4$), and pure motor ($n = 2$). Subclinical DSPN defined by abnormalities in any one of these parameters (with no or minimal signs/symptoms of neuropathy) was present in 18/51 (35.2%). Majority of them were post-pubertal ($n = 16/18$). HbA1c was significantly higher in the T1DM subgroup with abnormal NCS versus normal NCS (Table 1). However, there was no significant difference in age, gender, diabetes duration, and urine albumin-creatinine ratio (ACR) between the two groups (Table 1).

None of the children with T1DM had retinopathy. Five children had microalbuminuria (urine ACR > 30 μg/g creatinine on 2 occasions in the past 3 months). All five children having microalbuminuria also had subclinical neuropathy. NCS was abnormal in 13 out of 46 children with T1DM and no microalbuminuria.

Subclinical DSPN was found in a significant proportion (35%) of T1DM children. This study generated cut-offs to define subclinical DSPN from nerve conduction study data of a healthy cohort aged 5–18 years. This adds to the strength of the study as opposed to a previous study which might have overestimated the burden [5]. Using different criterion, Singh et al. reported subclinical DSPN in 56% of T1DM children, and CPN was most commonly affected [5].

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Table 1 Clinical and biochemical profile in T1DM with or without abnormal NCS

	T1DM with normal NCS ($n=33$)	T1DM with abnormal NCS ($n=18$)	p value
Age (years)	12.5 ± 3.4	13.3 ± 2.3	NS
Gender (male/female)	13/20	6/12	NS
Body mass index (kg/m^2)	17.8 ± 1.7	18.5 ± 0.9	NS
Diabetes duration (years)	5.8 ± 2.4	6.1 ± 3.1	NS
HbA1c (%)	8.3 (7.7–8.9) *	9.5 (8.9–10.1) *	0.01*
Creatinine (mg/dl)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	NS
Urine ACR (µg/g creatinine)	8.2 (3.2–13.2)	10.1 (3–17.8)	NS

*p value < 0.05 is considered significant. Data with normal distribution was presented as mean standard deviation, and nonparametric data was presented as median (inter-quartile range). Differences of continuous data between the two groups were assessed using the Student t-test or Mann–Whitney test as applicable. Difference in the proportion of categorical variable was assessed using the chi-square test. Statistical analysis was performed using SPSS version 22

Abbreviations: T1DM, type 1 diabetes mellitus; *NCS*, nerve conduction studies; *ACR*, albumin-creatinine ratio

However, the present study found that the sural nerve was the most common nerve affected, thereby suggesting that sensory neuropathy precedes motor neuropathy in agreement with previous studies [6, 7]. The findings further suggested that subclinical neuropathy is common in T1DM children even in absence of microalbuminuria or retinopathy.

Author contribution MB and MB extracted relevant clinical data and wrote the first draft. PM and SG edited the manuscript. SG is the corresponding author. All the authors approved the final version of the manuscript.

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Data Availability The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Declarations

Conflict of interest The authors declare no competing interests.

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CASE REPORT

The youngest patient with hemi-chorea and diabetic ketoacidosis as presenting manifestation of type 1 diabetes mellitus from India

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Abstract

Background Type 1 diabetes mellitus (T1DM) is one of the most common endocrine diseases in children. Majority of them present with metabolic crises in the form of diabetic ketoacidosis (DKA) at diagnosis. Various levels of encephalopathy and seizures are the well-known manifestation of DKA.

Case presentation We are reporting an 8-year-old girl who presented with hemi-chorea with DKA as a manifestation of type 1 DM which is extremely rare in literature in Asian subcontinents and has been encountered at such a young age for the first time in India.

Conclusion T1DM with metabolic crises should always be one of the important differentials of hemi-chorea in children.

Keywords Type 1 DM · DKA · Hemi-chorea

Introduction

Lately, T1DM has been on the rise like type 2 diabetes. Three new cases of T1DM/100,000 children 0–14 years of age are seen in India per year [1]. These children usually get diagnosed when they present with DKA, an acute metabolic crisis with varying degrees of encephalopathy. However, it is extremely rare for a child to present with movement disorder at the time of diagnosis. Though some studies have reported adults presenting with variety of movement disorders due to impaired glycemic control (hypo/hyper-glycemia), similar instances in paediatric age have been scarce [2]. We report the youngest girl who presented with acute hemi-chorea as a first manifestation of type 1 DM due to DKA.

Case presentation

An 8-year-old previously healthy female child presented to our emergency department with history of sudden onset of abnormal, slow, involuntary movements involving both right upper and lower limbs, which increased during activity and disappeared in sleep for 5 days. She also had history of behavioural changes in the form of increased irritability, drowsiness and confusion for one week.

She had no history of fever, headache, seizures and neurological illnesses in the past. She was not receiving any medication at the time of illness or before. Her birth had been uneventful, and she had normal development with good academic performance.

On clinical examination, the young girl appeared conscious, well oriented but irritable with blood pressure of 106/78 mm Hg. She had involuntary rhythmic quasi-purposive movements of right limbs involving upper limbs more than lower. She had near continuous right-sided movements resembling hemi-chorea which used to get explosive in character during anxiety and voluntary movements making it difficult for her to sit or walk. Her higher functions and cranial nerve examination were normal. There was hypotonia of both upper and lower limbs with no signs of meningeal irritation or cerebellar involvement. Her other systemic examination was normal.

Initially, clinical diagnosis of acute hemi-chorea secondary to auto-immune disorder like rheumatic chorea, systemic lupus erythematosus (SLE) Vs vascular stroke was suspected. However, upon further enquiry, she was found to have typical history of weight loss, polyphagia, polydipsia and polyuria over the last 15 days. Routine investigations revealed BSL (blood sugar level): 474 mg/dl with metabolic acidosis having anion gap of 9.2 mmol/dl with positive ketone bodies (serum (5.1) and urine (80 mg/dl)) indicating

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hyper-glycemic ketoacidosis. MRI revealed (Fig. 1) left-sided basal ganglia (caudate and lentiform nucleus) signal which was hyper-intense on T2-weighted and hypo-intense on T1 images suggestive of metabolic aetiology. Other supportive investigations revealed HBa1c – 16.5 and positive anti-GAD antibodies (137.2) with low C peptide (0.40 ng/ml) further confirming the diagnosis of T1DM.

The child was managed efficiently with BSPED 2020 protocol for DKA. Glycemic control was achieved after 48 h with correction of acidosis and dyselectrolemia. She was conscious, alert and active throughout her stay in the hospital. Her chorea became less severe enabling her to walk and stand without support on day 2 of treatment and betterment of blood sugar levels. She was discharged on subcutaneous insulin, oral tetrabenazine with minimal residual chorea but ambulant status. At the last follow-up after 2 months of discharge, there was no focal neurological manifestations with good compliance with T1DM management. MRI was not repeated due to financial constraints.

Discussion

Type 1 diabetes mellitus (T1DM) is the most common endocrine disorder of children with auto-immune aetiology. Recently, the number of cases of T1DM has increased significantly and we find 3 new cases per 100,000 children of 0–14 years. The peak age at diagnosis is 12 years with girls getting more affected than boys [3]. It may be auto-immune or idiopathic in nature and is present in 9% cases of insulin deficiency. The absence of insulin results in increased concentrations of glucose in the blood (hyper-glycemia) for the elimination of which there is increased water consumption to enable filtration from the kidney leading to a cycle of polydipsia and polyuria until insulin is finally administered. The reduced glucose uptake owing to lack of insulin causes the cells to use fats and proteins for energy which also produces ketones. Diabetic ketoacidosis (DKA) is therefore a common presentation of T1DM. Most children in the US with new onset of T1DM present with the classic signs and symptoms of hyper-glycemia and 30% with (DKA).

Neurologic manifestations, however, are relatively rare and mostly include lethargy, decreased level of consciousness and coma because of DKA. Extreme rarely chorea, cerebellar ataxia, weakness of lower limbs due to sciatic neuropathy leading to atrophy, hemi-paresis like symptoms have also been reported in literature associations of T1DM [4].

Chorea is a continuous spontaneous involuntary movement of distal muscles occurring during rest and activity which tends to disappear in sleep. Hemi-chorea is chorea involving only one side of the body. They are usually seen in lesions of the basal ganglia, tumours of the brain and metabolic, vascular, or degenerative disease. In rare instances, hemi-chorea has also been reported in type 2 DM in adults over 50 years [5]. However, it is extremely rare in the paediatric age group and less than 10 cases have been reported so far over the world but few from India [4, 6].

The exact pathogenesis of this manifestation is obscure, but there has been hypothesis that during hyper-glycemia there is a shift of cerebral metabolism to the anaerobic pathway with the inactivation of the tricarboxylic acid cycle [7]. The brain then uses GABA as an alternative source of energy which eventually leads to metabolic acidosis. In ketotic hyper-glycemia, GABA can be re-synthesized using ketone bodies, whereas GABA and acetate are depleted rapidly in non-ketotic hyper-glycemia-reducing acetylcholine synthesis

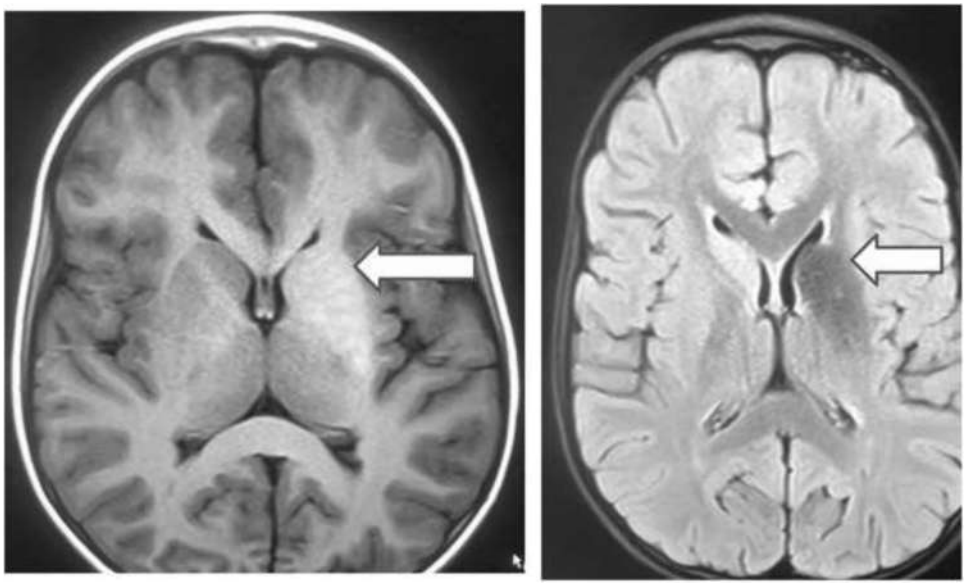

Fig. 1 MRI brain showing hypo-intensities on T1-weighted images and hyper-intensities on T2-weighted images in the left caudate and putamen

due to acetate depletion. Reduction of GABA and acetylcholine (inhibitory neurotransmitters) in the basal ganglia with associated metabolic acidosis and the lack of energy production is thought to cause a basal ganglia dysfunction and subsequent chorea [5]. Another proposed theory attributes occurrence of chorea to hyper-glycemia-induced hyper-viscosity leading to reduced regional cerebral blood flow [8]. Analyses of biopsy specimen of basal ganglia have revealed changes similar to infarction in the form of neuronal loss, gliosis and reactive astrocytosis [9]. These histological changes are also responsible for characteristic MRI signal intensities. Since all the proposed mechanisms are due to hyper-glycemia, the correction of blood sugar levels has shown amelioration of neurological symptoms and sometimes complete resolution of chorea [10]. Nevertheless, there are instances where additional antipsychotics have been required. In a meta-analysis of 53 adults with chorea and non-ketotic hyper-glycemia, 16 had complete resolution only with glycemic control, 31 needed treatment with haloperidol ($n = 18$) and others in combination ($n = 13$), though 7 patients had fluctuating course and were resistant to therapy. No such research has been done in paediatric population as of now.

Imaging studies may/not reveal any changes. Common involvement although has been seen in the basal ganglia especially the putamen and caudate nucleus in the form of hyper-intensities which interestingly resolve after correction of hyper-glycemia [11].

Conclusion

T1DM is a common disorder in the paediatric age group. Majority of them are diagnosed at DKA at emergency unit needing intensive care. Hemi-chorea has been reported extremely rarely with T1DM. This study emphasizes the need for considering it as one of the differentials of acute hemi-chorea which needs immediate attention and prompt treatment.

Abbreviations T1DM: Type one diabetes mellitus; DKA: Diabetic ketoacidosis; Hg: Mercury; GAD: Glutamic acid decarboxylase autoantibodies; SLE: Systemic lupus erythematosus; GABA: Gamma aminobutyric acid; BSPED: Britsh Society for Paediatric Endocrinology and Diabetes

Author contribution AVB helped conceptualized the idea, literature search and summarising concept, discussion and summarising.

VK helped in case summary and discussion of case report.

TP helped in conceptualization and discussion.

All contributed (AVB, VK, TP) in editing and approving the article.

Data Availability Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Taken.

Competing interests The authors declare no competing interests.

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ORIGINAL ARTICLE

Evaluation of progression in metabolic parameters along with markers of subclinical inflammation and atherosclerosis among normoglycemic first degree relatives of type 2 diabetes mellitus patients

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Abstract

Background The aim of this study is to assess for the change in progression of inflammatory, adiposity, and atherosclerotic markers in first degree relatives of type 2 diabetes mellitus patients.

Methods Normal glucose tolerant (NGT) individuals (20–40 years) who had positive family history of T2DM (FHP) were enrolled in this prospective study based on ADA 2015 criteria. Age, sex, and BMI matched controls without any history of diabetes in their parents referred as family history negative (FHN) were taken for comparison. At baseline, detailed clinical assessment and requisite blood/imaging investigations were done. All the available subjects from the original cohort (FHN-32 and FHP-46) were studied after 2 years with recording of the clinical, biochemical and imaging parameters.

Results A total of 64 cases (FHP) and 42 controls (FHN) were enrolled at baseline. FHP group had significantly higher hsCRP ($p = 0.039$) and cIMT ($p = 0.003$) than that of FHN group. No significant difference in the rate of conversion of NGT to prediabetes (using multiple criteria) was found after 2 years between the two groups. cIMT was increased significantly from baseline in FHP group than FHN group at the end of the study(0.02 ± 0.03 vs. 0.01 ± 0.02 mm, $p = 0.002$). But there was no significant difference for changes in glycemic status, lipid parameters, HOMA IR, hsCRP, and adiposity markers between the two groups at the end of the study.

Conclusion Despite no significant differences in change in glycemic parameters or rates of conversion from NGT to pre diabetes, cIMT increased significantly in the normoglycemic offspring of T2DM subjects than those without history of T2DM in their parents.

Keywords Insulin resistance · High sensitive C reactive protein (hsCRP) · Visceral adiposity · First degree relatives · Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia and its detrimental effects on major organ systems. The etiopathogenesis of T2DM is complex and is still incompletely understood despite decades of research. Interaction between the genetic and environmental factors is incriminated in the development of T2DM in a susceptible individual. The risk of development of T2DM is around 40% for offspring having history of T2DM in one parent whereas it is almost 70% if both parents are affected [1]. Obesity plays a major role in accentuating the risk of T2DM in susceptible individuals.

Insulin resistance plays a major role in the pathogenesis of metabolic syndrome as well as T2DM and is

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transmissible from parent to their offspring [2]. So the metabolic consequences of insulin resistance may be demonstrated in the first degree relatives of T2DM subjects before they develop overt diabetes. It is well evident that in most populations, those who evolve into frank T2DM usually demonstrate insulin resistance at an earlier time [3]. To overcome this insulin resistance, increased secretion of insulin occurs from the pancreatic beta cell resulting in hyperinsulinemia, which is capable of maintaining a relatively normal glucose tolerance state. However, in a subpopulation of these subjects impaired glucose tolerance (IGT) develops eventually as the hyperinsulinemic response is insufficient to fully compensate for the prevailing insulin resistant state. The proportion of conversion of IGT subjects to frank T2DM depends on the ethnicity of the individuals studied and the assay methods used. In the Chennai Urban Rural Epidemiology Study(CURES) after a follow-up of 10 years, conversion rate of NGT to prediabetes and diabetes was 25.7% and 19.4% respectively [4]. In this study, family history of diabetes was one of the major predictors of progression to dysglycemia [4].

Inflammatory cytokines are implicated in the pathogenesis of T2DM [5]. But it is uncertain whether inflammation causes insulin resistance, or is a secondary effect of obesity itself [6]. C-reactive protein (CRP), a nonspecific inflammatory marker, is most strongly associated with the development of T2DM [7]. However, the causal association has not been proved conveniently yet [8].

Apart from genetic factors, obesity (visceral adiposity in particular), has been incriminated in the development of insulin resistance and T2DM [9]. Increased flux of free fatty acid (FFA) into the circulation from the visceral adipose tissue is mainly responsible for insulin resistance [10]. Visceral obesity has also been associated with increased production of various adipocytokines, reduction of insulin sensitivity and an increased risk for development of diabetes as well as dyslipidemia [11]. Non-diabetic offspring of T2DM subjects have been found to have increased abdominal fat content and making them more prone for the development of various cardiometabolic diseases [12]. Ultrasound (USG) is a cost-effective and reliable method for the measurement of abdominal fat with a very good diagnostic accuracy compared with that of computerized tomography (CT) scan [13].

The risk of coronary heart disease (CHD) development is increased in their offspring of diabetic parents [14]. Differences in the body composition and metabolic and cardiovascular parameters may be responsible for this triggering effect. Carotid intima media thickness (cIMT) assessment is a well-studied tool and can be used as an indicator for future development of cardiovascular diseases like myocardial infarction and stroke [15]. Various studies have revealed a comparatively higher degree of subclinical inflammation and visceral adiposity in the offspring of T2DM subjects than that of nondiabetic parents [14, 16]. There is limited data available regarding the progression of glycemic status, inflammatory markers, and cIMT in first degree relatives of T2DM individuals in our population and hence the current prospective study was carried out.

Material and methods

Normal glucose tolerant (NGT) adults belonging to 20–40 years [family history positive (FHP)] were recruited at baseline. Age, sex, and body mass index (BMI) matched controls without any history of T2DM in their parents and relatives up to third generation were taken for comparison [family history negative (FHN)]. Individuals with history of hypertension, cardiac disease, stroke, smoking, dyslipidemia, renal disease, liver disease, thyroid illness, presence of any acute infection/illness, connective tissue disorder, chronic medication intake, polycystic ovary syndrome, pregnancy, and lactation were excluded from the study.

A total of 100 healthy individuals (aged 20–40 years) with a parental history of T2DM were enrolled. Similarly, around 100 healthy individuals without parental history were also enrolled to serve as control. All enrolled individuals underwent detailed screening tests as per inclusion and exclusion criteria for fulfilling eligibility for the study. NGT was detected as per the American Diabetic Association (ADA) guideline, i.e., fasting plasma glucose (FPG) < 100 mg/dl, 2-h post glucose plasma glucose (PGPG) < 140 mg/dl, and HbA1C < 5.6% [17]. Only euglycemic healthy adults were recruited at baseline (total = 106) which was based on sample size derived from earlier available literature. This group consisted of 64 in FHP group and 42 in FHN group. After baseline clinical, biochemical and radiological investigations, all subjects were asked to review at periodic intervals. At the end of the study (after 2 years), detailed clinical, biochemical, and imaging parameters were recorded for all available subjects of original cohort (46 in FHP group and 32 in FHN group) (Fig. 1).

All participants had undergone detailed clinical examinations to look for physical signs like acanthosis nigricans or skin tags. Body weight, height, waist circumference, hip circumference, and blood pressure were measured. Measurement of height and weight were done by using a standard apparatus. The point midway between the lowest rib margin and the iliac crest was taken for the measurement of waist circumference, whereas hip circumference was assessed along the widest portion of buttocks. BMI was calculated by using the formula as weight in kg divided by the height in m2. After resting for at least 5 min, measurement of blood pressure was done by using a mercury sphygmomanometer in supine position.

A standard 75 g oral glucose tolerance test (OGTT) with FPG, 2 h PGPG, and HbA1C testing were done in each subject after an overnight fast for at least 8 h.

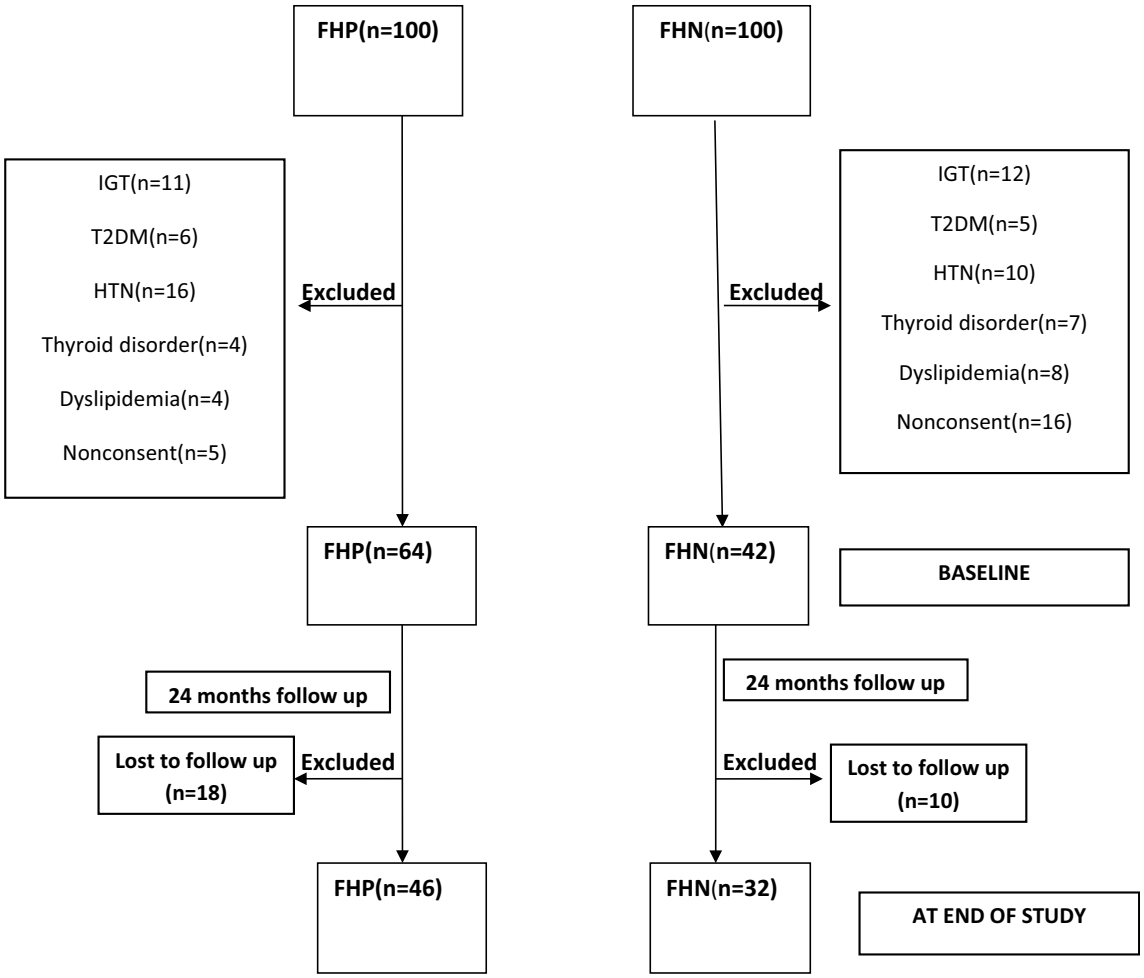

Fig. 1 Flow diagram depicting study design

Estimation of lipid profile [serum total cholesterol (TC), TG, LDL, HDL], fasting insulin and hsCRP were performed by taking the fasting blood sample in the morning. The plasma glucose was estimated with glucose oxidase-peroxidase method. Serum total cholesterol was measured by cholesterol esterase oxidase peroxidase method and TG by colormetric enzymatic method. HDL was estimated by direct enzymatic method. LDL was calculated by using Friedewald formula [18]. High-pressure liquid chromatography (HPLC) was used for HbA1C estimation. Serum insulin was estimated by chemiluminescent microparticle immunoassay (CMIA) method and nephelometry method was used for the measurement of serum hsCRP. For detection of insulin resistance, Homeostasis Model Assessment of Insulin Resistance (HOMA IR) was calculated by using the formula as [FPG (mg/dl) × fasting insulin (mU/L)]/405 [19].

Carotid intima media thickness (cIMT) was estimated by using high resolution B mode ultrasound with electrical linear transducer (5 to 9 MHz). Measurement was done in supine position at a point just proximal to the carotid bulb in the common carotid arteries with patient's head turned slightly to the contra lateral side. Mean value of the bilateral measurements was taken for reporting the cIMT. Measurement of subcutaneous tissue thickness denoted as SAT was done by taking the vertical distance from skin to the linea alba with a 9 L transducer (2.5 to 8.0 MHz). Similarly, visceral adipose tissue thickness denoted as VAT was estimated as the vertical distance from the peritoneum up to the front edge of the lumbar vertebra with a 5C transducer (1.5 to 4.5 MHz) [20]. Both SAT and VAT were measured three times and the average of the three readings was taken for reporting. The recording of the images was done by a single radiologist who was blinded regarding the group allocation.

At the end of the study, body weight, height, waist circumference, hip circumference, and blood pressure were measured in all available subjects in both groups. Glycemic status was evaluated in all subjects by doing a 75 g OGTT and HbA1C testing. Lipid profile, fasting insulin, hsCRP, cIMT, VAT, and SAT were also measured in each subject at the end of the study. Prediabetes and diabetes mellitus (DM) were detected by using ADA guideline (2015) criteria, i.e., prediabetes:FPG-

100–125 mg/dl (IFG) or 2 h PGPG-140–199 mg/dl (IGT) or HbA1C- 5.7–6.4% and DM: FPG ≥ 126 mg/dl or 2 h PGPG ≥ 200 mg/dl or HbA1C ≥ 6.5% or RPG ≥ 200 mg/dl with symptoms of diabetes [17].

Statistical analysis

Mean and standard deviation were used to summarize the continuous variables. Categorical data were reported as percentages or proportions. Normality distribution was assessed by using Shapiro-Wilk test. Nonparametric tests (Mann-Whitney *U* test) and parametric tests (independent *t* test) were performed for comparison between the variables. Data analysis was done by IBM SPSS 21 statistical software (IBM Corp., Armonk, NY, USA).

Results

At baseline, total number of individuals recruited in FHP group and FHN group were 64 and 42 respectively. FHP group had a mean age of 28.31 ± 4.91 years as that of 28 ± 4.23 years in FHN group ($p = 0.538$). There was no significant difference with regards to physical activity, BMI, blood pressure, and WHR between the two groups. However, mean total cholesterol and LDL levels were significantly higher in the FHP group than that of FHN group ($p < 0.01$ for both). No significant difference was observed with regards to glycemic parameters like FPG, 2 h PPG, and HbA1C between the two groups at baseline (*p*-non significant). We also did not find any significant difference in insulin resistance markers (fasting insulin and HOMA IR) and adiposity indices (SAT, VAT) ($p > 0.05$ for each parameter) between the two groups. However, individuals in the FHP group had significantly elevated hsCRP ($p = 0.039$) and cIMT ($p = 0.003$) than that of FHN group at baseline.

To look for progression of various metabolic parameters, inflammatory markers, insulin resistance, and intima media thickness in both FHP and FHN individuals, reassessment of these individuals was done (after 2 years). Ten subjects in FHN group and 18 subjects in FHP group were lost to follow-up during this period. Hence, comparison was made between 32 subjects and 46 subjects in FHN group and FHP group respectively (Fig. 1). Four subjects (8.7%) in FHP group and two subjects (6.25%) in FHN group transitioned into IFG from NGT based on FPG criteria respectively ($p = 1.000$). Similarly based on 2 h PGPG criteria, four subjects (8.7%) in FHP group and two subjects (6.25%) in FHN group transitioned into IGT from NGT ($p = 1.000$). During the same period, 11 subjects (23.91%) in FHP group and six subjects (18.75%) in FHN group became pre-diabetic based on HbA1C recommended criteria ($p = 0.78$) (Fig. 2). Hence, it was observed that numerically higher number of individuals met the criteria of pre diabetes from FHP group versus FHN group but statistical significance was not achieved. Similarly, we noted that there was no significant difference in the change (Δ) in BMI, WHR, and blood pressure (SBP, DBP) from baseline to the end of the study among the two groups. The two groups did not differ significantly in terms of change in glycemic status (FPG, 2 h PGPG, and HbA1C) and lipid parameters (TG, LDL, and HDL) from base line (Table 1). Also, HOMA-IR did not change significantly from baseline in FHP group (1.25 ± 3.46 vs. 0.32 ± 0.61, $p = 0.056$). We also noted that hsCRP was not significantly changed from baseline in both groups at the end of the study (*p*-non significant for change). No significant change in adiposity markers like SAT (0.08 ± 0.19 vs. 0.04 ± 0.12 cm, $p = 0.159$) and VAT (0.33 ± 0.42 vs. 0.22 ± 0.22 cm, $p = 0.213$) from baseline was observed in FHP group in comparison to FHN group. However, cIMT was increased significantly from baseline in FHP group in comparison to FHN group at the end of the study (0.02 ± 0.03 vs. 0.01 ± 0.02 mm, $p = 0.002$) (Table 1).

Discussion

We have previously reported certain noteworthy differences in our population with regards to inflammation, markers of insulin resistance, adiposity indices, and cIMT between non diabetic offspring of T2DM patients and age, sex, and BMI matched controls without having history of T2DM in their parents [21]. We found that cIMT was significantly higher in the offspring of T2DM patient [21]. This finding has been also reported by earlier studies suggesting that possibly genetic predisposition may accelerate the development of atherosclerosis [22–25].

Similarly, we found that the first degree relatives of T2DM patients had significantly higher hsCRP levels than controls in our population [21]. This finding of chronic low-grade inflammation in normoglycemic subjects with parental history of T2DM has been observed in other studies including one from Indian subcontinent [22, 24]. It may be plausible that this chronic low-grade inflammation might accentuate atherosclerosis risk in T2DM patients' offspring. Certain important perturbations in lipid metabolism have been reported among normoglycemic offspring of parents with T2DM which include elevated TG and increased total cholesterol and LDL with decreased HDL levels [21].

Importantly and interestingly, we did not observe any significant difference with regard to glycemic status, insulin resistance or blood pressure between the first degree relatives of T2DM subjects and controls at baseline [21]. Similar to our study, few authors also did not find any significant difference in glycemic parameters, degree of insulin resistance (HOMA IR), or blood pressure in the offspring of T2DM subjects than those without having diabetic history in their parents [10, 22,

Table 1 Comparison of anthropometric, biochemical, hormonal, and radiological parameters in FHP and FHN groups at the end of the study

Parameters	Change from baseline (Δ)		*p* value for change (Δ)
	FHN group (*n* = 32)	FHP group (*n* = 46)	
BMI (kg/m^2)	0.76 ± 0.99	0.71 ± 1.08	0.764
WHR	0.03 ± 0.06	0.03 ± 0.05	0.545
SBP (mmHg)	1.56 ± 4.94	3.52 ± 5.35	0.135
DBP (mmHg)	1.63 ± 3.95	1.26 ± 3.51	0.652
FPG (mg/dL)	5.03 ± 4.98	7.93 ± 8.02	0.073
2hrPGPG (mg/dL)	9.94 ± 22.43	7.09 ± 20.33	0.633
HbA1C (mmol/mol)	2.51 ± 1.79	2.62 ± 3.14	0.859
TC (mg/dl)	10.31 ± 6.1	9.36 ± 16.23	0.160
TG (mg/dl)	10.88 ± 13.09	8.98 ± 15.6	0.089
LDL (mg/dl)	9.47 ± 7.59	8.48 ± 14.74	0.163
HDL (mg/dl)	-0.34 ± 4.01	-0.7 ± 3.35	0.866
hsCRP (mg/L)	0.66 ± 0.8	0.61 ± 1.36	0.388
Fasting insulin (mIU/L)	0.88 ± 2.69	4.43 ± 13.9	0.111
HOMA IR	0.32 ± 0.61	1.25 ± 3.46	0.056
SAT (cm)	0.04 ± 0.12	0.08 ± 0.19	0.159
VAT (cm)	0.22 ± 0.22	0.33 ± 0.42	0.213
cIMT (mm)	0.01 ± 0.02	0.02 ± 0.03	**0.002**

Data are expressed as mean ± S.D, $p < 0.05$- significant

BMI body mass index, *WHR* waist hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *PGPG* post glucose plasma glucose, *TC* total cholesterol, *TG* triglyceride, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *hsCRP* high sensitive C-reactive protein, *HOMA IR* homeostasis model assessment for insulin resistance, *VAT* visceral adipose tissue thickness, *SAT* subcutaneous adipose tissue thickness, *cIMT* carotid intima media thickness

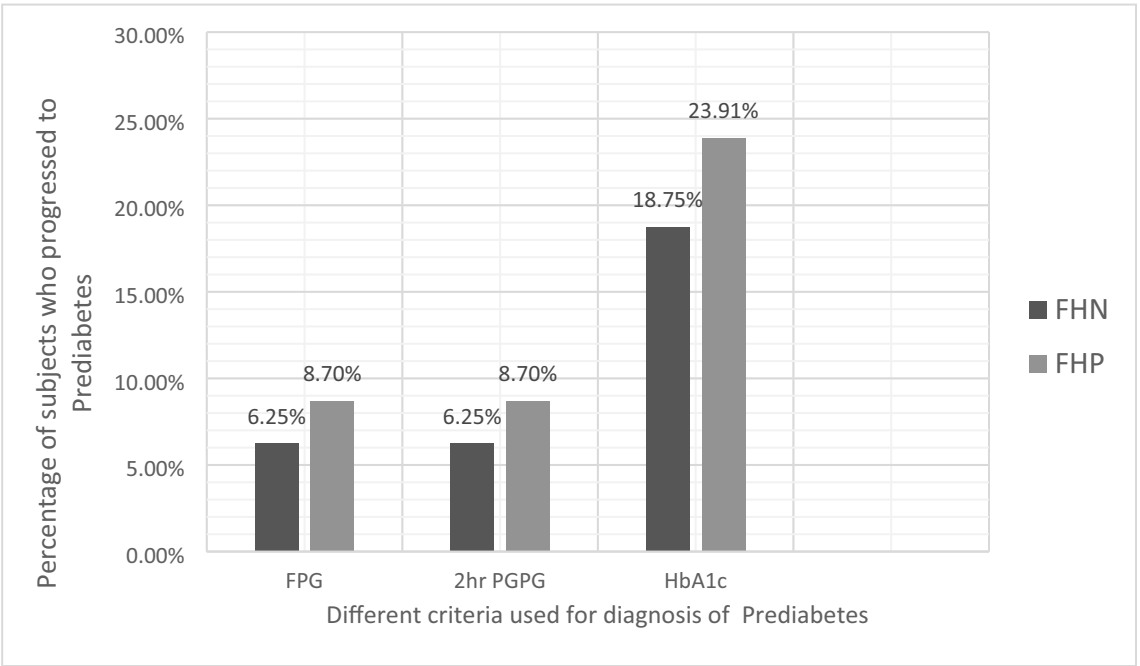

Fig. 2 Progression to prediabetes in FHP and FHN groups at the end of the study. *FPG* fasting plasma glucose, *PGPG* post glucose plasma glucose

23]. However, Ustun et al. reported significantly higher fasting blood glucose, blood pressure, serum insulin, and HOMA IR levels in the offspring of T2DM patients [24].

To look for progression of various metabolic indices including glycemic parameters, insulin resistance, and intima media thickness in both FHP and FHN individuals, we evaluated all available subjects from the original cohort at the end of the study. However, after a follow-up of 2 years, there was no significant difference for change (Δ) in glycemic status (FPG, 2hrPGPG & HbA1C) and insulin resistance marker (fasting insulin, HOMA IR) between the two groups at the end of the study. Moreover, no significant difference in the rate of conversion of NGT to IGT, IFG, or T2DM between FHP and FHN individuals was noted. In the Chennai Urban Rural Epidemiology Study(CURES) after a follow-up period of 10 years, conversion rate of NGT to prediabetes and diabetes was 25.7% and 19.4% respectively [4]. In our study, we evaluated the individuals after 2 years which is much shorter duration to look for the conversion of NGT to IGT or DM than the previous Indian study [4]. Similarly, an Iranian study carried out in the offspring of T2DM subjects reported the progression rate from NGT to IFG, IGT and diabetes were 8.6%, 3.7%, and 0.5% per year after a follow-up period of 27.6 months, respectively [26].

Our previous findings suggested no significant differences in adiposity indices among FHP and FHN subjects. FHP subjects had similar levels of SAT as well as VAT in comparison to that of FHN individuals [21]. In agreement to our findings, Kriketos et al. also did not find any significant difference in subcutaneous as well as visceral adipose tissue depots in the first degree relatives with history of T2DM in their parents [10]. Apart from genetic factors, central adiposity may play a role in the development of insulin resistance. In this study (after completion of follow-up period), no significant difference in the change from baseline for adiposity markers (SAT/VAT) between the two groups was found.

As previously discussed, we reported significantly higher cIMT and hsCRP among FHP subjects than FHN subjects in our cohort at baseline. Hence, it was worthwhile to explore whether any difference in progression of cIMT would be observed between these two groups. Surprisingly, we found that cIMT was increased significantly from baseline in FHP group in comparison to FHN group even in a relatively short span of 2 years. In the IMPROVE study, Baldassarre et al. found significant progression of cIMT in subjects with three or more vascular risk factors to the tune of 0.005 mm/year during the first 15 months of follow-up [27]. In the PROG-IMT Collaboration study, it was found that the average annual mean cIMT progression was 0.009 mm/year in T2DM patients, whereas the progression was 0.010 mm/year in the non-diabetic individuals [28]. No significant difference for hsCRP change (Δ) was observed at the end of the study between the two groups.

The limitations of the study include a relatively small sample size limiting the generalizability of our results. Only hsCRP was assessed as surrogate inflammatory marker. We used USG for the measurement of adiposity indices instead of CT or MRI. We have preferred USG because it is inexpensive and non-ionizing and adiposity indices measurement can be done in the same sitting along with the cIMT assessment. However, study of hepatic steatosis/fibrosis was not done. The study follow-up period is short, i.e., 2 years, which may be insufficient to look for the progression of NGT to either IGT or DM. Lastly, many confounding factors like diet pattern, recruitment based on parental diabetic history, and physical activity level have not been adequately studied during follow-up. However, despite these limitations, we have reported data of these two matched groups in a prospective fashion which would be definitely helpful in understanding influence of family history of T2DM on progression of various metabolic parameters in our population.

In conclusion, our study reports that T2DM subject's offsprings have significantly elevated hsCRP levels and increased cIMT than those without diabetic history in their parents at baseline. There were no significant differences with regards to change of glycemic parameters or rates of conversion from NGT to pre diabetes among the two groups. In contrast to above finding, cIMT increased significantly in the normoglycemic offspring of T2DM subjects than those without history of T2DM in their parents. Hence, perhaps mere presence of family history of T2DM in normoglycemic individuals may result in important metabolic perturbations and differential progression of atherosclerotic process in this vulnerable population. These findings may have significant bearing on their future cardiovascular health status.

Declarations

Ethics approval and consent to participate Written informed consent was obtained from the study participants and institutional ethical committee clearance was taken.

Conflicting interest Nil.

Financial disclosure All authors have no financial relationship related to this article to disclose.

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ORIGINAL ARTICLE

Improvement of biochemical and hematological parameters in alloxan-induced diabetic rats via administration of ethanol extract of *Garcinia kola* seeds

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Abstract

Background *Garcinia kola* (Gluttiferae) is recommended traditionally for the management of diabetes in Nigeria. This present study evaluated the effect of the ethanol extract of *G. kola* seeds on the biochemical and hematological status of alloxan-induced diabetic rats.

Methods Rats were divided into six groups of five rats each. Diabetes was induced in groups 2–6 by intraperitoneal injection of alloxan monohydrate (130 mg/kg bwt.). Group 1 served as normal control, group 2 was left untreated, group 3 was treated with 2.5 mg/kg bwt. glibenclamide (standard drug), and groups 4–6 were given an oral administration of 100, 300, and 500 mg/kg body weights of extract for 21 days. Fasting blood samples were collected at baseline, day 0, 7, 14, and 21 for blood glucose evaluation. Biochemical and hematological parameters were also investigated at the end of treatment.

Results The extract produced the best effects at 500 mg/kg bwt. Blood glucose concentration was significantly ($p < 0.05$) reduced from days 7 to 21. A reduction from 390.50 ± 28.21 in diabetic rats to 60.50 ± 2.96 mg/dl was observed on day 21. The extract also lowered the total cholesterol (TC), triacylglycerol (TAG), low-density lipoprotein (LDL), and malondialdehyde (MDA) concentrations from 259.64 ± 52.22, 74.41 ± 15.39, 162.81 ± 48.44, and 57.75 ± 2.06 mg/dl to 120.32 ± 24.25, 41.05 ± 0.00, 82.31 ± 20.26, and 37.25 ± 2.21 mg/dl respectively. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities were significantly increased from 31.25 ± 12.50, 33.59 ± 5.94, and 0.50 ± 0.01 IU/L to 68.75 ± 12.50, 81.52 ± 4.16, and 1.07 ± 0.15 IU/L respectively. Red blood cell (RBC) count was restored from 192.50 ± 28.72 to 271.25 ± 47.32 ($\times 10^9$). At 100 mg/kg bwt., white blood cell (WBC) count was also normalized from 8000.00 ± 2648.26 to 12800.00 ± 365.14 ($\times$ 10 mm^3).

Conclusion *G. Kola* seeds possess antidiabetic activity and capability of restoring aberrated biochemical and hematological indices in diabetic rats. This research therefore consolidates its traditional use for the management of diabetes mellitus.

Keywords *Garcinia kola* · Diabetes mellitus · Alloxan · Glibenclamide · Antioxidant · Hematology

Introduction

Diabetes mellitus is a metabolic disorder marked by persistent hyperglycemia, a high level of glucose [1], and it occurs as a result of insulin deficiency or malfunctioning [2]. It is among the most chronic diseases and widely prevalent worldwide [3]. Statistics show that 2.8% of the global populations are burdened with this disease and it is likely to increase above 5.4% by 2025 [2]. World Health Organization (WHO) recently classified diabetes into type 1, type 2, gestational, hybrid forms, unclassified, and other specific types of diabetes [4]. Hyperglycemia and other underlying pathogenic mechanisms

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such as dyslipidemia, immune dysfunction, excessive reactive oxygen species (ROS) production, and hypertension culminate in chronic complications of diabetes [5, 6]. These complications are commonly microvascular and macrovascular in nature and include retinopathy, neuropathy, nephropathy, angiopathy, cardiovascular diseases, and diabetic foot [5, 7]. Simulating diabetes mellitus in experimental animal models presents a safer alternative to sourcing for therapeutic interventions while avoiding unnecessary and ethically challenging studies in humans [8]. Alloxan and streptozotocin are the most important and commonly used chemical compounds for the induction of diabetes mellitus in experimental animals. Alloxan is primarily used for short-term diabetes studies which last for about 4 weeks, while streptozotocin can be used for both short- and long-term diabetes studies—lasting for up to 3 months [9]. Both alloxan and streptozotocin are capable of destroying beta cells and inducing type 1 diabetes mellitus. Streptozotocin is also used for the experimental induction of type 2 diabetes mellitus using fat-fed streptozotocin-treated, fructose-fed streptozotocin-injected, and nicotinamide-streptozotocin models [10]. The rapid increase in diabetes globally necessitates the search for new antidiabetic agents from natural plants that will not only restore normoglycemia but also ameliorate diabetic complications.

The use of plants in traditional medicine is as old as man. Plant parts such as leaves, seeds, roots, and bark have been highly exploited as food, medicine, and for other essential purposes [11]. The array of active compounds derived from plants play a significant role in exerting pharmacological properties such as anti-inflammatory, antibiotics, anti-parasitic, antioxidant, analgesics, and hormonal [12]. Apart from these activities, plants also play a major role in the discovery of new drug leads for the treatment of diabetes mellitus. The antidiabetic potentials of African medicinal plants such as, *Aloe vera*, *Clausena anisata*, *Cymbopogon citratus*, *Morinda lucida*, *Buchholzia coriacea*, *Picralima nitida*, *Lagerstroemia speciosa*, *Bridelia ferruginea*, *Sclerocarya birrea*, *Ageratum conyzoides*, *Ceiba pentandra*, and *Persea americana* have been demonstrated [13]. *Garcinia kola* Heckel is also a promising plant for the treatment of diabetes. It is a dicotyledonous plant which belongs to the Gluttiferae family and largely distributed in the tropical rain forests of Central and West Africa [14]. It is also known as bitter kola, false kola, and male kola [15]. It is an evergreen tree, medium-sized, about 15–17 m tall with a fairly narrow crown, simple and shiny leaves spotted with resin glands [16]. *G. kola* is referred to as "wonder plant" since almost all its parts are extensively used in herbal medicine to treat a variety of ailments ranging from common cold to hepatitis [14–16]. *G. kola* has reportedly shown anti-inflammatory, anti-microbial, hepatoprotective, antioxidant, anti-ulcer, anti-cancer, anti-hypertensive, and a myriad of other bioactivities [16, 17]. The antidiabetic potential of *G. kola* has also been investigated, with focus on its ability to ameliorate hyperlipidemia in diabetic rats [18–21]. Since anemia is a blood-related complication of diabetes, mainly due to insufficient production of erythropoietin by the kidney [22], this research further investigated the effect of *G. kola* seeds on hematological parameters of alloxan-induced diabetic rats.

Materials and methods

Plant collection

The seeds of *G. kola* used for this study were purchased from Ogige main market, Nsukka, Enugu State, and were identified by Mr. Alfred Ozioko of the International Center for Ethnomedicine and Drug Development (InterCEDD), Nsukka, Enugu State, Nigeria, where the voucher specimen (InterCEDD/022010) was deposited.

Plant preparation and extraction

Dirt and sand were removed from *G. kola* seeds by washing them with clean water, after which they were drained, and chopped. The seeds were shade-dried for several days and subsequently pulverized into fine powder. The powdered *G. kola* seeds (500 g) were macerated in 1.5 L of ethanol for 48 h. The suspension was thereafter filtered with Whatman no. 4 filter paper and the filtrate concentrated using a rotary evaporator (Model Modulyo 4K, England) to yield the extract.

Animals

Adult male Wistar albino rats of between 10 and 16 weeks with weights of 100–180 g were maintained at the Animal House of the Department of Biochemistry, Faculty of Biological Sciences, University of Nigeria, Nsukka. The rats were acclimatized under standard laboratory condition with 12-h light/dark cycle for 1 week prior to the commencement of the experiment. They were given regular feed (commercial Rodent Chow, Vital Feeds Nig. Ltd.) and had access to clean drinking water ad libitum.

Experimental design

Wistar albino rats were randomly divided into 6 groups of 5 rats each and treated as shown below:

Group 1: Control (Normal rats)
Group 2: Alloxan-induced diabetic rats (untreated rats)

Group 3: Alloxan-induced diabetic rats treated with 2.5 mg/kg bwt of glibenclamide (standard drug)
Group 4: Alloxan-induced diabetic rats treated with 100 mg/kg bwt. of ethanol extract of *G. kola* seed
Group 5: Alloxan-induced diabetic rats treated with 300 mg/kg bwt. of ethanol extract of *G. kola* seed
Group 6: Alloxan-induced diabetic rats treated with 500 mg/kg bwt. of ethanol extract of *G. kola* seed

Induction of diabetes

Baseline blood glucose levels were determined prior to diabetes induction in the rats. Rats were fasted overnight before the intraperitoneal injection of 130 mg/kg bwt. of alloxan monohydrate (Sigma-Aldrich, USA) that was dissolved in iced cold normal saline. Rats with blood glucose levels greater than 200 mg/dl after 5 days (day 0) were considered diabetic and randomly distributed into groups for the study. Oral administration of the different doses of the extract—100, 300, and 500 mg/kg bwt. — and glibenclamide (Nigerian-German Chemicals Plc, Nigeria) commenced on day 0 after distribution into groups. Treatment was done once per day and lasted for twenty-one (21) days during which blood glucose levels were determined on days 7, 14, and 21. After the 21-day treatment period, rats were anesthetized, sacrificed, and blood collected via cardiac puncture. Whole blood was used for the hematological analysis while serum was separated by centrifugation for other biochemical assays. Assays were carried out immediately after blood and serum collection.

Determination of blood glucose concentration

Fasting blood sugar was determined using Accu-check active glucometer (Roche Diagnostics, USA) according to the method of Marks and Dawson [23].

Lipid profile parameters

Total cholesterol (TC) was determined using the method of Allain et al. [24], high-density lipoprotein-cholesterol (HDL) was determined using the method of Albers et al. [25], while low-density lipoprotein-cholesterol (LDL) concentration was determined using the method of Assmann et al. [26], all as contained in QCA commercial kits. Triacylglycerol (TAG) was carried out using the method of Albers et al. [25] as contained in Randox commercial kit.

Antioxidant enzymes

Superoxide dismutase (SOD) activity was determined using the method of Xin et al. [27]. The activity of catalase (CAT) was determined according to the method of Aebi [28]. Glutathione peroxidase (GPx) activity was assayed using the modified method of Paglia and Valentine [29].

Lipid peroxidation

Lipid peroxidation was assessed by measuring the concentration of the lipid peroxidation product, malondialdehyde (MDA) spectrophotometrically as described by Varshney and Kale [30].

Hematological indices

Hemoglobin (Hb) concentration was measured using the method of Kelly [31]. Packed cell volume (PCV) and red blood cell (RBC) count were determined following the method of Schalm et al. [32], while the white blood cell count (WBC) was carried out using standard techniques as described by Ramnik [33].

Statistical analysis

Data obtained were analyzed using Statistical Product and Service Solutions (SPSS), version 20.0. Test of statistical significance was carried out using one-way analysis of variance (ANOVA), and data were subjected to least significant difference (LSD) post hoc test for multiple comparisons. The results were expressed as mean ± standard error of mean (SEM). Mean values with $p < 0.05$ were considered significant.

Results

Fasting blood glucose levels

The fasting blood glucose levels were significantly ($p < 0.05$) higher in the untreated diabetic animals than in the normal control (Table 1). Oral administration of ethanol extract of *G. kola* seeds and glibenclamide significantly ($p < 0.05$) decreased the blood glucose concentration from day 7 compared to the diabetic untreated rats.

Serum lipid profile parameters

Table 2 shows that the TC, TAG, and LDL concentrations of alloxan-induced diabetic untreated rats significantly ($p < 0.05$) increased while the HDL concentration significantly ($p < 0.05$) decreased compared to the normal control. Administration of the ethanol extract of *G. kola* seeds caused a significant ($p < 0.05$) reduction in TC, TAG, and LDL concentrations compared to the

Table 1 Effect of ethanol extract of *Garcinia kola* seeds on blood glucose concentration

Groups	Duration of glucose estimation (mg/dl)				
	Baseline	Day 0	Day 7	Day 14	Day 21
Group 1	70.50 ± 7.24	79.75 ± 6.54	78.00 ± 7.15	78.25 ± 6.41	79.25 ± 5.65
Group 2	65.00 ± 6.25 (0.548)	292.75 ± 26.85* **(0.005)**	374.25 ± 30.70* **(<0.0001)**	384.75 ± 28.24* **(<0.0001)**	390.50 ± 28.21* **(<0.0001)**
Group 3	74.00 ± 5.49 (0.329)	342.75 ± 83.50 (0.459)	210.25 ± 30.77** **(0.002)**	106.00 ± 27.90** **(<0.0001)**	88.75 ± 21.88** **(<0.0001)**
Group 4	83.50 ± 6.59 (0.054)	243.25 ± 20.75 (0.463)	173.00 ± 30.52** **(<0.0001)**	139.50 ± 33.88** **(<0.0001)**	131.75 ± 32.81** **(<0.0001)**
Group 5	100.25 ± 6.54** **(0.001)**	208.25 ± 44.01 (0.217)	153.75 ± 15.53** **(<0.0001)**	119.75 ± 5.81** **(<0.0001)**	72.75 ± 12.89** **(<0.0001)**
Group 6	77.50 ± 5.81 (0.181)	275.50 ± 54.62 (0.797)	226.25 ± 55.77** **(0.004)**	153.50 ± 15.54** **(<0.0001)**	60.50 ± 2.96** **(<0.0001)**

Values represent mean ± SEM; (n = 5). *Significant difference compared with group 1, **significant difference compared with group 2 ($p < 0.05$, ANOVA). p values are represented in parenthesis; bold values indicate a statistically significant difference. Group 1: control (normal rats). Group 2: positive control (diabetic untreated rats). Group 3: standard control (alloxan-induced diabetic rats + 2.5 mg/kg bwt of glibenclamide). Group 4: alloxan-induced diabetic rats + 100 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 5: alloxan-induced diabetic rats + 300 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 6: alloxan-induced diabetic rats + 500 mg/kg bwt. of ethanol extract of *G. kola* seed

untreated group. However, no significant increase in HDL concentration was observed.

Antioxidant indices

There was significant ($p < 0.05$) reduction in CAT activity and significant increase in MDA level of diabetic untreated rats compared with the normal rats. Treatment with the ethanol extract of *G. kola* showed a dose-dependent significant ($p < 0.05$) increase in the activities of SOD, CAT, and GPx compared with the diabetic untreated rats (Table 3). MDA concentration was also significantly decreased compared to the untreated group.

Hematological indices

Relative to the normal control, there were significant ($p < 0.05$) reductions in the RBC and WBC counts of

Table 2 Effect of ethanol extract of *Garcinia kola* seeds on serum lipid profile parameters

Groups	Lipid profile indices (mg/dl)			
	TC	TAG	HDL	LDL
Group 1	208.98 ± 12.66	43.61 ± 5.13	38.74 ± 17.20	102.52 ± 2.41
Group 2	259.64 ± 52.22* **(0.038)**	74.41 ± 15.39* **(<0.0001)**	21.45 ± 1.41* **(0.022)**	162.81 ± 48.44* **(0.033)**
Group 3	221.64 ± 24.25 (0.111)	59.26 ± 15.23** **(0.039)**	38.74 ± 11.41** **(0.022)**	131.10 ± 52.16 (0.240)
Group 4	113.99 ± 25.33** **(<0.0001)**	43.61 ± 5.13** **(<0.0001)**	25.33 ± 2.98 (0.582)	79.94 ± 25.45** **(0.005)**
Group 5	132.99 ± 37.99** **(<0.0001)**	46.18 ± 5.92** **(0.001)**	32.78 ± 11.41 (0.119)	90.97 ± 44.96** **(0.013)**
Group 6	120.32 ± 24.25** **(<0.0001)**	41.05 ± 0.00** **(<0.0001)**	32.05 ± 2.85 (0.143)	82.31 ± 20.26** **(0.006)**

Values represent mean ± SEM; (n = 5). *Significant difference compared with group 1, **significant difference compared with group 2 ($p < 0.05$, ANOVA). p values are represented in parenthesis; bold values indicate a statistically significant difference. Group 1: control (normal rats). Group 2: positive control (diabetic untreated rats). Group 3: standard control (alloxan-induced diabetic rats + 2.5 mg/kg bwt of glibenclamide). Group 4: alloxan-induced diabetic rats + 100 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 5: alloxan-induced diabetic rats + 300 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 6: alloxan-induced diabetic rats + 500 mg/kg bwt. of ethanol extract of *G. kola* seed. *TC* total cholesterol, *TAG* triacylglycerol, *HDL* high-density lipoprotein-cholesterol, *LDL* low-density lipoprotein-cholesterol

Table 3 Effect of ethanol extract of *Garcinia kola* seeds on serum antioxidant indices

	Antioxidant indices			
Groups	SOD (IU/L)	CAT (IU/L)	MDA (mg/dl)	GPx (IU/L)
Group 1	43.75 ± 12.50	52.60 ± 2.87	40.75 ± 1.70	0.55 ± 0.25
Group 2	31.25 ± 12.50 (0.151)	33.59 ± 5.94* **(0.001)**	57.75 ± 2.06* **(<0.0001)**	0.50 ± 0.01 (0.596)
Group 3	50.00 ± 0.00** **(0.037)**	46.36 ± 6.78** **(0.019)**	45.50 ± 1.73** **(<0.0001)**	0.95 ± 0.04** **(<0.0001)**
Group 4	56.25 ± 12.50** **(0.008)**	50.30 ± 8.24** **(0.003)**	40.00 ± 1.41** **(<0.0001)**	0.74 ± 0.09** **(0.019)**
Group 5	62.50 ± 14.43** **(0.001)**	61.95 ± 10.87** **(<0.0001)**	44.00 ± 1.63** **(<0.0001)**	0.86 ± 0.46** **(0.001)**
Group 6	68.75 ± 12.50** **(<0.0001)**	81.52 ± 4.16** **(<0.0001)**	37.25 ± 2.21** **(<0.0001)**	1.07 ± 0.15** **(<0.0001)**

Values represent mean ± SEM; (n = 5). *Significant difference compared with group 1, **significant difference compared with group 2 ($p < 0.05$, ANOVA). *P* values are represented in parenthesis; bold values indicate a statistically significant difference. Group 1: control (normal rats). Group 2: positive control (diabetic untreated rats). Group 3: standard control (alloxan-induced diabetic rats + 2.5 mg/kg bwt of Glibenclamide). Group 4: alloxan-induced diabetic rats + 100 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 5: alloxan-induced diabetic rats + 300 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 6: alloxan-induced diabetic rats + 500 mg/kg bwt. of ethanol extract of *G. kola* seed. *SOD* superoxide dismutase, *CAT* catalase, *MDA* malondialdehyde, *GPx* glutathione peroxidase

untreated diabetic group. WBC count of the extract-treated groups increased significantly ($p < 0.05$) compared to the untreated group. RBC count of group 6 also increased significantly ($p < 0.05$) compared to the untreated group. No significant difference in PCV and Hb was observed (Table 4).

Discussion

Ethanol extract of *G. kola* seeds significantly restored the blood glucose concentration and the altered lipid and antioxidant parameters in diabetic rats. The extract also exhibited significant normalization of the RBC and WBC of diabetic Wistar rats.

Table 4 Effect of ethanol extract of *Garcinia kola* seeds on hematological indices

	Hematological indices			
Groups	PCV (%)	Hb (g/dl)	RBC ($\times 10^9$)	WBC ($\times 10$ mm^3)
Group 1	47.50 ± 3.10	16.15 ± 1.05	281.25 ± 62.76	12900.00 ± 1321.61
Group 2	44.75 ± 2.87 (0.409)	15.46 ± 1.12 (0.548)	192.50 ± 28.72* **(0.018)**	8000.00 ± 2648.26* **(<0.0001)**
Group 3	44.50 ± 6.65 (0.940)	15.13 ± 2.26 (0.768)	190.00 ± 58.02 (0.942)	9100.00 ± 1089.34 (0.333)
Group 4	44.25 ± 1.50 (0.880)	15.04 ± 0.51 (0.712)	241.25 ± 29.54 (0.170)	12800.00 ± 365.14** **(<0.0001)**
Group 5	48.00 ± 5.41 (0.331)	16.32 ± 1.84 (0.454)	223.75 ± 52.34 (0.372)	10500.00 ± 1509.96** **(0.036)**
Group 6	45.00 ± 5.77 (0.940)	15.30 ± 1.96 (0.884)	271.25 ± 47.32** **(0.033)**	12650.00 ± 1526.43** **(0.001)**

Values represent mean ± SEM; (n = 5). *Significant difference compared with group 1, **significant difference compared with group 2 ($p < 0.05$, ANOVA). *P* values are represented in parenthesis; bold values indicate a statistically significant difference. Group 1: control (normal rats). Group 2: positive control (diabetic untreated rats). Group 3: standard control (alloxan-induced diabetic rats + 2.5 mg/kg bwt of Glibenclamide). Group 4: alloxan-induced diabetic rats + 100 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 5: alloxan-induced diabetic rats + 300 mg/kg bwt. of ethanol extract of *G. kola* seed. Group 6: alloxan-induced diabetic rats + 500 mg/kg bwt. of ethanol extract of *G. kola* seed. *PCV* packed cell volume, *Hb* hemoglobin, *RBC* red blood cell, *WBC* white blood cell count

Hyperglycemia in diabetes results from deficiency in insulin secretion, insulin action, or both. As used in the present study, alloxan induces diabetes by damaging pancreatic β-cells, resulting in decreased release of endogenous insulin [34]. This consequently leads to decreased utilization of glucose by the tissues, leading to increases in blood glucose level as observed after diabetes induction (Table 1). In a manner similar to glibenclamide, significant reduction in blood glucose concentration as a result of the administration of *G. kola* seeds was observed in this study from days 7 to 21. This effect was most significant at 500 mg/kg bwt of the extract on day 21 (Table 1). This is attributable to the stimulation of insulin which enhances glucose uptake into the cells. This glucose-lowering effect could also be due to the inhibition of carbohydrate-metabolizing enzymes such as α-glucosidase by *G. kola* seeds as previously demonstrated [35], thereby reducing post-prandial blood glucose levels. Kolaviron, a biflavonoid complex from *G. kola*, has also been shown to inhibit carbohydrate-metabolizing enzymes and intestinal glucose absorption, and increase muscle glucose uptake from the blood [36]. These processes are additional mechanisms by which *G. kola* exhibits its antidiabetic actions, thus corroborating the observed findings.

Diabetes mellitus induces cardiomyopathy which is associated with dyslipidemia—an aberration in lipid metabolism [6]. According to ADA [37], in adults with diabetes, the optimal LDL cholesterol levels should be less than 100 mg/dl (2.60 mmol/L), optimal HDL cholesterol levels should be more than 40 mg/dl (1.02 mmol/L), and triglyceride levels of less than 150 mg/dl (1.7 mmol/L) is desirable. Increase in the TC, TAG, and LDL concentrations and a decrease in the HDL concentration of the untreated diabetic rats were observed in this study after alloxan induction (Table 2). The observed increase in serum lipids could be due to an increase in the mobilization of free fatty acids from peripheral tissues as a result of the activation of hormone-sensitive lipase during insulin insufficiency [18]. *G. kola* seed extract significantly decreased TC, TAG, and LDL concentrations better than glibenclamide (Table 2). Contrarily, glibenclamide completely reversed HDL concentration while the seed extract exhibited no significant changes on HDL (Table 2). The ability of the biflavonoid fractions of the root bark, stem bark, and seed of *G. kola* to reduce the concentrations of TC, TG, and LDL has been demonstrated [38], with the seed fraction exhibiting the most significant effects. Also, the biflavonoid fraction of the seed produced no significant impact on HDL concentration in consonance with this study. This finding was however in contrast to previous research [20]. Alteration of the lipid parameters is indicative of the extract potential in modulating diabetic dyslipidemia.

As with many other diseases, oxidative stress has also been implicated in the pathogenesis of diabetes [7]. Pancreatic beta cells are susceptible to oxidative damage due to the essential oxidative metabolism required for glucose-stimulated insulin secretion (GSIS). This process generates free radicals and also suppresses antioxidant defense system in β-cells [39]. Free radical formation in diabetes increases lipid peroxidation of polyunsaturated fat in cell membrane and damages other cell components [7] leading to diabetic complications; ROS may react with transition metals such as iron or copper to form stable lipoperoxidation-derived aldehydes such as malondialdehydes that damage cell membranes [40]. Excess ROS also causes insulin resistance by negatively regulating insulin signaling [40]. In the alloxan model of diabetes used in this study, the activities of the antioxidant enzymes were decreased in the diabetic untreated group compared to the normal rats, while MDA concentration was significantly increased (Table 3). Ethanol extract of *G. kola* seeds significantly restored these observed aberrations, in line with the recent research on the ability of kolaviron to overturn these parameters in hypertensive rats [41]. The increase in the activity of antioxidant enzymes in this study implies increased mopping up of ROS, thereby eliminating their cytotoxic effects.

Blood composition undergoes alterations in a diseased state, such as diabetes [42]. Hyperglycemia-induced anemia occurs as a result of increased non-enzymatic glycosylation of RBC membrane protein and glycation of hemoglobin [43], reducing the RBC and Hb levels of diabetic rats. Alloxan-induced diabetes resulted in a significant decrease in RBC and WBC, while the decrease in PCV and Hb were not significant (Table 4) in accordance with a previous study [44]. This could be due to the effects of alloxan on rapidly dividing hemopoietic cells and suppression of hematopoiesis due to insulin deficiency, which results as β-cells are selectively damaged by alloxan [45]. Decrease in RBC is also attributable to increased non-enzymatic glycation of RBC membrane proteins due to hyperglycemia. RBC count was normalized at 500 mg/kg bwt. of *G. kola* seed extract. The extract was also effective in normalizing the reduced WBC count induced by elevated blood glucose. On the other hand, glibenclamide produced no significant effect on the altered RBC and WBC counts. Improvement in WBC count suggests immune-boosting capacity of the extract. Since ROS have also been found to be involved in the mechanism of diabetes and RBC hemolysis [43], the increase in RBC count could be attributed to the antioxidant property of *G. kola*. Previous findings showed that *G. kola* seed powder (GKP) significantly increased WBC and RBC in comparison to this study [46].

Determining the biochemical and hematological parameters on weekly basis would have been a better design to effectively monitor the antidiabetic activity of *G. kola* seeds. This will help ascertain the particular week in which the modification of each parameter commenced. The dose(s) of the extract responsible for the weekly changes can also be monitored. Nevertheless, this study gave scientific credence to the claim that *G. kola* has both hypoglycemic and lipid attenuating

effects. It also demonstrated that *G. kola* seed extract has a positive effect on the hematological and antioxidant status of alloxan-induced diabetic rats especially at 500 mg/kg bwt., thereby restoring normoglycemia. Hence, it could be recommended as a promising source of alternative diabetic therapeutics, through further research involving the isolation and bioactivity study of its antidiabetic principles.

Declarations

Research involving animals This research followed all applicable international, national, and institutional guidelines for the care and use of laboratory animals. The ethical approval was granted by the Ethics and Biosafety Committee, Faculty of Biological Sciences, University of Nigeria, Nsukka (UNN/FBS/EC/1038).

Conflict of interest The authors declare no competing interests.

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CORRECTION

Correction to: Improvement of biochemical and hematological parameters in alloxan-induced diabetic rats via administration of ethanol extract of *Garcinia kola* seeds

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The corrections in the Abstract lines 13 and 15 was not carried out correctly.
The Original article has been corrected.

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ORIGINAL ARTICLE

Association of serum osteocalcin with beta cell function, insulin resistance, and glycemic parameters in south Indian type 2 diabetic subjects

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Abstract

Background Osteocalcin (OC), also known as bone Gla (gamma-carboxyglutamic acid) protein, is a marker of bone formation. OC has effect on glucose and fat metabolism. Role of OC in type 2 diabetes mellitus (T2DM) is not well studied in Indian population. Our study aimed to see the relationship between OC and parameters of glucose metabolism in type 2 diabetes mellitus.

Methods This cross-sectional study included 120 subjects with T2DM. In each subject, fasting insulin, serum osteocalcin (measured by ELISA), fasting plasma glucose (FPG), post prandial plasma glucose (PPG), and glycated Hb (HbA1c) were measured. HOMA 2.0 model was used to measure insulin resistance (HOMA-IR) and β-cell function (HOMA-β). Then, serum osteocalcin levels were correlated with HOMA-IR, HOMA-β, FPG, PPG, and HbA1c.

Results Serum OC levels reduced with increase in insulin resistance (HOMA-IR) ($r = -0.274$, $p = 0.004$); however, there was no association with the beta cell function. OC had negative association with FPG ($r = -0.14$, $p = 0.12$) and PPG ($r = -0.123$, $p = 0.18$); however, it was statistically insignificant. Glycated hemoglobin (HbA1c) was significantly reduced in diabetic patients with higher OC levels ($r = -0.208$, $p = 0.025$).

Conclusion Serum OC has significant association with insulin resistance and HbA1c in subjects with T2DM, which might suggest possible role of serum OC in glucose metabolism in T2DM.

Keywords Beta cell function · Fasting plasma glucose · Glycated hemoglobin · Insulin resistance · Post prandial plasma glucose · Type 2 diabetes

Highlights
1. Serum osteocalcin decreases significantly as insulin resistance (HOMA-IR) increases in subjects with type 2 diabetes mellitus.
2. Glycated hemoglobin (HbA1c) was significantly reduced in diabetic patients with higher serum osteocalcin levels. FPG and PPG were also reduced, though it was insignificant.

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Introduction

As mammals evolved, they have developed paracrine, autocrine, and endocrine signaling pathways that regulate the energy metabolism in the metabolically active tissues. The bone, which is mainly the structural tissue of the body, has been recently recognized to be having endocrine role. Evidence from mice and clinical studies suggests that many regulatory molecules released from the bone modulate glucose metabolism and are called "osteokines." The first such osteokine recognized to link bone and glucose metabolism is osteocalcin (OC), which functions in its active form, that is, undercarboxylated OC (ucOC) [1]. In 2007, the Karsenty group was the first to demonstrate that circulating ucOC regulates whole-body energy metabolism mainly glucose metabolism [2].

Osteocalcin is a 49-residue (5–9 kda) polypeptide and is incorporated into the bone matrix. But 10–40% of osteocalcin produced is not incorporated into the bone matrix and is postulated that newly synthesized osteocalcin is released into the circulation as the intact (1–49) molecule and acts on pancreas [3, 4]. Normal level of circulating osteocalcin in serum ranges from 5 to 25 ng/ml [3]. Osteocalcin deficient mice showed hyperglycemia and glucose intolerance, decreased β-cell proliferation and insulin secretion, and decreased insulin sensitivity [2]. So, the osteocalcin has a role in regulating glucose homeostasis, but its role in pathogenesis of diabetes is not known clearly, though there are speculative models.

There are studies on western population which show the association of OC with parameters of glucose metabolism, but there is a paucity of the data in Indian population. So, we undertook this study to find out the relationship between serum osteocalcin and parameters of glucose metabolism in a south Indian population.

Methods

This study was a cross-sectional, observational, single center study, conducted at Kasturba Hospital, Manipal, Karnataka. The study subjects included were in-patients and out-patients with type 2 diabetes mellitus [as per ADA criteria [5]] above 18 years and below 80 years of age. The study period was from January 2018 to June 2019.

The study subjects who were eligible were included into the study (after providing detailed patient information sheet and after obtaining informed consent) as per the following inclusion and exclusion criteria:

- Inclusion criteria—all type 2 diabetes mellitus subjects [as per ADA criteria [5]] above 18 years and below 80 years of age were included.
- Exclusion criteria:

i. Subjects who are on vitamin K and its inhibitors, vitamin D and calcium, steroids, anti-epileptic drugs, statins, calcitonin, bisphosphonate, estrogen, and thiazolidonediones, SGLT2i known to affect bone metabolism [6].
ii. Subjects having pancreatic gland dysfunction (example: pancreatitis and traumatic injury to pancreas), chronic liver disease, musculoskeletal disorders (example: bone metastases, hypercalcemia of malignancy, multiple myeloma, and inflammatory arthritis), hypoparathyroidism and hyperparathyroidism, and chronic kidney disease with mineral bone disease.
iii. Patients with fracture or previous history of fracture and risk factor for osteoporosis like smoking and alcohol consumption were excluded.

Sample size was estimated by using the following formula:

$$n^* = \left(Z_{1-alpha/2} + Z_{1-beta\ C}\right)/C$$

where $C = \frac{1}{2}\, l_n(1 + r / 1 - r)$; $n = n^* / 1 - R$.

Assuming the correlation of coefficient for osteocalcin and HOMA-β to be $r = 0.4$, $R^2 = 0.6$, for 80% power and 5% level of significance, the minimum number required is approximately 120.

In total, 120 subjects were part of the study. The subjects were asked questions as per a standard, structured proforma regarding comorbidities and complications pertaining to type 2 diabetes mellitus. All patients underwent basic anthropometry measurement which included height and weight. Body mass index (*BMI*) was calculated using the formula (Quetelet index), $BMI = weight\ (\text{kg}) / [height\ (\text{m})]^2$.

Waist circumference was measured midway between inferior margin of ribs and the superior border of iliac crest at the end of normal expiration (as per WHO STEPS protocol) [7]. Waist circumference (WC) of ≥ 90 cm for males and ≥ 80 cm for females was considered as abnormal (as per IDF criteria) [8]. Hip circumference (HC) was measured at the widest portion of the buttocks with the tape parallel to the floor. WC (in cm) was divided by HC (in cm) to calculate waist to hip ratio (WHR). Blood was collected by venipuncture after overnight fasting and 2 h after standard meal. Plain vacutainers, fluoride vacutainers, and EDTA vacutainers were used for collecting serum, plasma, and whole blood samples, respectively. Samples were allowed to clot in plain vacutainers for 30 min. Venous blood was then centrifuged at 3500 rpm for 10 min to separate plasma and serum from RBCs. FPG and PPG were measured in respective plasma samples. Serum to assess fasting insulin, serum osteocalcin was stored at −80 and was analyzed on a later date. Beta cell function and insulin resistance was then calculated using HOMA calculator version 2.2 which uses the homeostatic model assessment (HOMA) 2 model for estimation [9, 10].

FPG, PPG, and HbA1c were measured by using fully automated biochemical analyzer (Roche cobas). Fasting insulin was measured by DRG insulin ELISA kit (batch number 44K018/01-2019 ETA-2935 manufactured by DRG International, Inc., USA) and serum osteocalcin was measured by DIAsourceHOST-ELISA kit (batch number 181001/04-2019 KAP138, manufactured by DIAsourceImmunoAssays S.A., Rue du Bosquet, 2, B-1348 Louvain-la-Neuve, Belgium). Detection limit of the serum osteocalcin kit is 0.08 ng/ml and the normal range for the same is 5 to 25 ng/ml.

The precision of the serum osteocalcin kit is shown in Table 1.

Analysis was done by using SPSS software version 16.0. The data which are continuous and normally distributed were

Table 1 Precision of the serum osteocalcin kit

Intra assay				Inter assay			
Serum	*N*	<*X*> ± SD (ng/ml)	CV (%)	Serum	*N*	<*X*> ± SD (ng/ml)	CV (%)
AB	20	11.4 ± 0.5	4.7	AB	20	11.8 ± 0.4	3.5
	20	28.2 ± 0.28	3.1		20	27.7 ± 1.55	5.6

SD, standard deviation; *CV*, coefficient of variation

expressed as mean ± SD and the data which has skewed distribution expressed as median with interquartile range. Categorical data were expressed as percentage. Mann-Whitney *U* and Kruskal-Wallis tests were used to compare serum osteocalcin levels between groups. Pearson's correlation coefficient test was used to correlate the two continuous variables which were normally distributed. Spearman rank correlation coefficient test was used to correlate the two continuous variables which were not normally distributed (r = correlation coefficient). p value < 0.05 was considered as statistically significant.

Results

The general characteristics of the study population are mentioned in Table 2. The mean age of 120 diabetic subjects was 54.79 ± 11.28 years and out of them, 61 were female subjects and 59 were male subjects. Most of the subjects were obese, as the mean BMI of the study population was 26.95 ± 4.74 kg/m^2. The waist to hip ratio in male subjects was 1.00 ± 0.03 and 0.97 ± 0.06 in female subjects. The median duration of the diabetes of the study population was 3 (0, 10) years. The mean FPG was 155.07 ± 60.84 mg/dL, mean PPG was 223.42 ± 80.98 mg/dL, and mean HbA1c was 9.3 ± 2.1%. The median percentage of HOMA-β which is suggestive of beta cell function was 60.05 (33.75, 85.47) %. The median HOMA-IR which is indicative of insulin resistance was 1.74 (1.31, 2.70). The median serum osteocalcin level in the study population was 4.31 (2.55, 5.40) ng/ml.

There was a significant negative correlation of serum osteocalcin levels with the duration of diabetes (r = −0.229, p = 0.01). There was no association with BMI (r = −0.047, p = 0.60).

The FPG (r = −0.141, p = 0.126) and PPG (r = −0.123, p = 0.181) were decreased with the increase in serum osteocalcin levels, though the reduction was not statistically significant. HbA1c levels reduced significantly as the serum osteocalcin increased (r = −0.208, p = 0.025) (n = 116).

Osteocalcin reduced significantly with increase in insulin resistance (HOMA-IR) (r = −0.274, p = 0.004) and there was no association found between serum osteocalcin and beta cell function (HOMA-β) (r = 0.097, p = 0.29).

Table 2 General characteristics of the study subjects

Characteristics	Number of subjects (n = 120)
Age (years)	54.79 ± 11.28
Duration of diabetes (years)	3 (0, 10)
BMI (kg/m^2)	26.95 ± 4.74
Waist circumference [male] (cm)	90.15 ± 6.10†
Waist circumference [female] (cm)	92.59 ± 10.65†
Hip circumference [male] (cm)	89.49 ± 5.43†
Hip circumference [female] (cm)	94.92 ± 10.93†
Waist to hip ratio in males	1.00 ± 0.03†
Waist to hip ratio in females	0.97 ± 0.06†
FPG (mg/dL)	155.07 ± 60.84
PPG (mg/dL)	223.42 ± 80.98
HbA1c (%)	9.3 ± 2.1
Fasting insulin (μIU/ml)	12.30 (9.11, 18.27)
HOMA-β (%)	60.05 (33.75, 85.47)
HOMA-IR	1.74 (1.31, 2.70)
Serum osteocalcin (ng/ml)	4.31 (2.55, 5.40)
eGFR (ml/min/1.73 m^2)	92.4 ± 18.80

• *BMI*, body mass index; *FPG*, fasting plasma glucose; *PPG*, post prandial plasma glucose; *HbA1c*, glycated hemoglobin A1c; *HOMA-β*, beta cell function; *HOMA-IR*, insulin resistance; *eGFR*, glomerular filtration rate

• Normally distributed variables are presented as mean ± SD and skewed variables are presented as median (25th quartile, 75th quartile)

† • The total number of male subjects was n = 59 and females was n = 61

Table 3 shows the association of serum osteocalcin with diabetes duration and biochemical parameters. Scatter plots depicting association of serum osteocalcin with duration of diabetes, HOMA-IR, and HbA1c are shown in Figs. 1, 2, and 3, respectively.

Discussion

Until recently, bone was considered solely as structural tissue, without any effects on energy metabolism. Animal studies have proved that serum osteocalcin has effects on energy metabolism, particularly glucose metabolism [2, 11].

In our study, there was significant decrease in serum osteocalcin levels with the longer duration of diabetes (r = −0.229, p = 0.01). A similar finding was noted in a cross-sectional analysis by Takashi et al. on 50 Japanese subjects (r = −0.24 and p = 0.09) [12]. This inverse association between duration of diabetes and serum osteocalcin could be due to the slower rate of bone formation in subjects with diabetes; however, the results have been conflicting among the studies. A study on

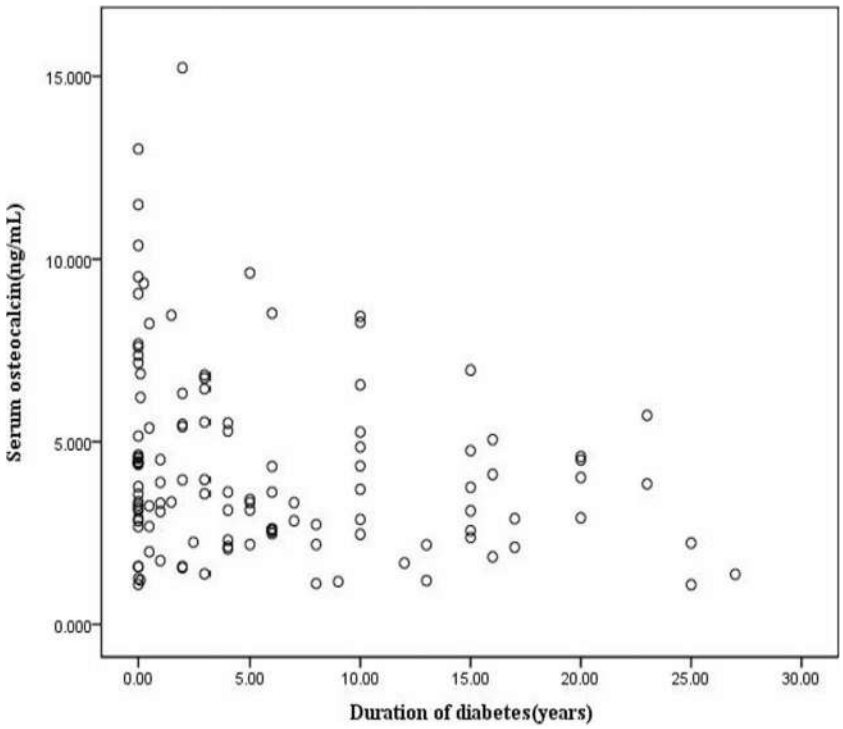

Fig. 1 Scatter plot showing significant negative association of serum osteocalcin levels with the duration of diabetes ($r = -0.229$, $p = 0.01$)

994 Japanese subjects by Kanazawa et al. [13] showed that there is no association between serum osteocalcin and duration of diabetes. A similar association was done by Sayinalp et al. and showed no association, but the study included only 27 Turkish men [14]. The varied results might be due to the confounding effect of other factors like age, gender, and BMI [15–17]. There was no significant association with BMI.

Clinical studies have shown significant increase of FPG with decrease in the serum osteocalcin levels. A case control

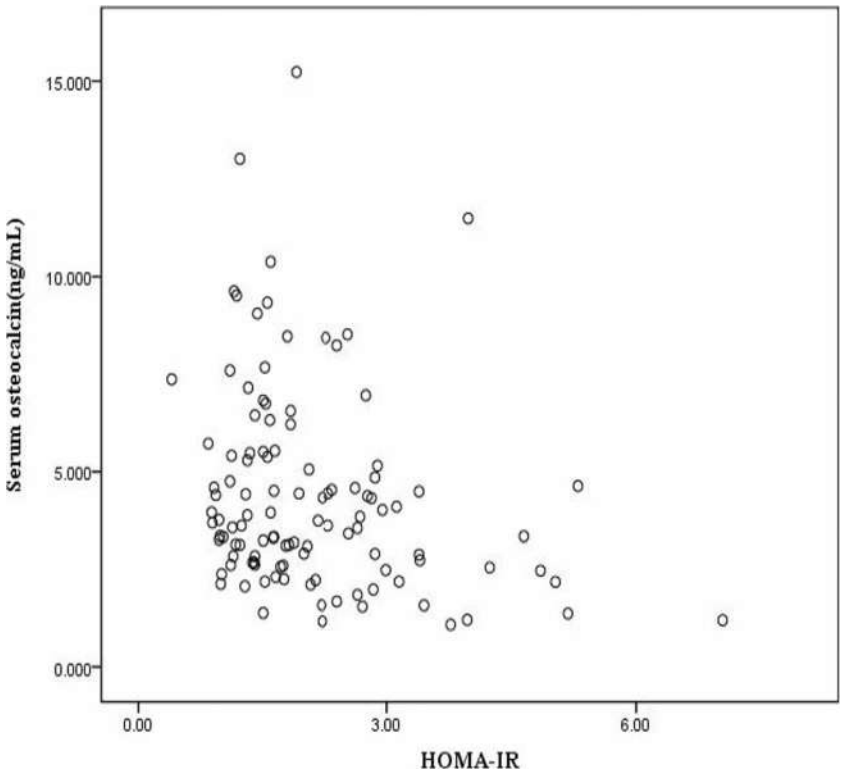

Fig. 2 Scatter plot showing significant negative association of serum osteocalcin with HOMA-IR (insulin resistance) ($r = -0.274$, $p = 0.004$)

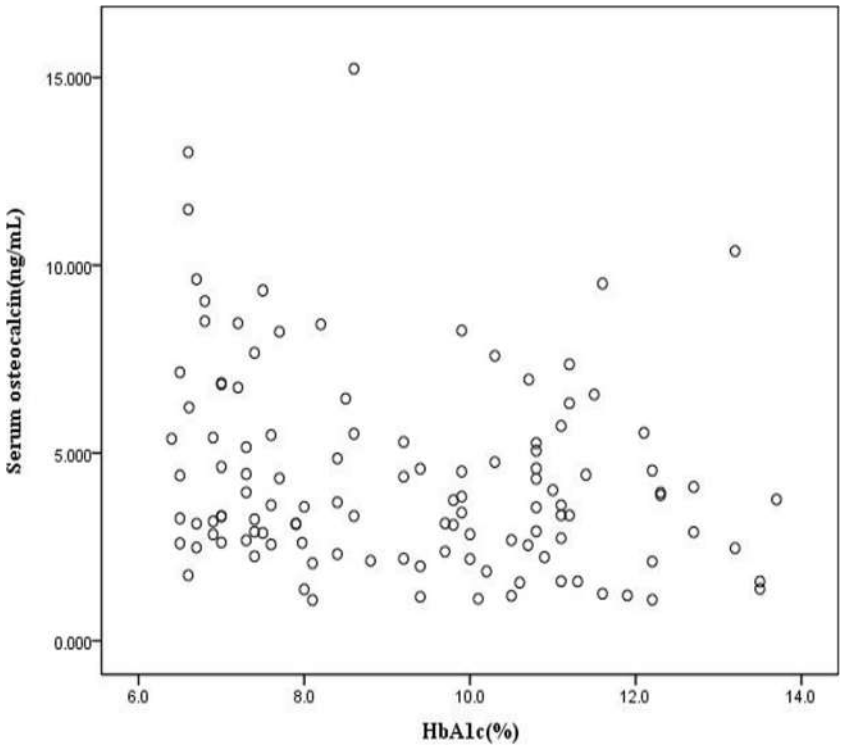

Fig. 3 Scatter plot showing significant negative association of serum osteocalcin with HbA1c ($r = -0.208$, $p = 0.025$)

study on elderly Sweden subjects by Kindblom et al. showed that serum osteocalcin was inversely related to fasting plasma glucose ($p < 0.001$) in both diabetic and non-diabetic subjects, i.e., FPG increased as osteocalcin level decreased and vice versa [18].

Hwang et al. conducted a cohort study on Korean middle aged subjects, which showed significant weak negative correlation of serum osteocalcin with FPG ($r = -0.202$, $p = 0.041$) [19]. Few other clinical studies also showed similar associations [20, 21]. Our study also showed that there was increase in fasting plasma glucose with the decrease in the serum osteocalcin levels, but did not reach the statistical significance.

In the literature, there are only few studies which used post prandial glucose as correlation parameter. In our study, the PPG increased with decrease in the serum osteocalcin levels or vice versa, but did not achieve a statistical significant relationship. Hwang et al. found negative association between serum osteocalcin and post prandial plasma glucose [19]. A study conducted by Zhou et al. on Chinese diabetic and normal glucose tolerant subjects showed that the PPG has inverse association with serum osteocalcin. However, the correlation coefficient, r, was −0.089 with significance level of 0.048 [22]. But Atsushi Aoki et al. had found a positive association between 2-h post load sugar levels with serum osteocalcin in Japanese subjects [23].

Our study showed that serum osteocalcin decreases over the period in individuals with type 2 diabetes mellitus with poor glycemic control or vice versa ($r = -0.208$, $p = 0.025$). Similar results were reported by Xiayo Ma et al. on Chinese individuals with type 2 diabetes has significant lower glycated hemoglobin with increased serum osteocalcin ($r = -0.419$, $p = < 0.01$) [24]. Another study on Japanese individuals by Iki et al. was consistent with the above finding [25]. A study by Zhou et al. on Chinese diabetic and normal glucose tolerant subjects showed HbA1c lower in patients with higher serum osteocalcin [22].

Table 3 Association of serum osteocalcin with diabetes duration and biochemical parameters

Parameter	r	p^*
Diabetes duration (years)	−0.229	0.010
HOMA-β (%)	0.097	0.290
HOMA-IR	−0.274	0.004
HbA1c (%)	−0.208	0.025
FPG (mg/dL)	−0.141	0.126
PPG (mg/dL)	−0.123	0.181
BMI (kg/m^2)	−0.047	0.60

• *HOMA-β*, beta cell function; *HOMA-IR*, insulin resistance; *HbA1c*, glycated hemoglobin A1c; *FPG*, fasting plasma glucose; *PPG*, post prandial plasma glucose; *BMI*, body mass index

• Pearson's correlation coefficient test was used to correlate the two continuous variables which were normally distributed. Spearman rank correlation coefficient test was used to correlate the two continuous variables which were not normally distributed

• r = correlation coefficient

* • p value < 0.05 was considered as statistically significant

In the current study, we observed that serum osteocalcin decreased significantly with increase in insulin resistance (p = 0.004). Our finding was consistent with the following mentioned studies. A cross-sectional study by Sarkar et al. on 108 central Indians with newly detected diabetes found significant negative association of osteocalcin with HOMA-IR (p = 0.001) when compared to healthy controls after doing linear regression analysis and adjusting with age, gender, BMI, and waist to hip ratio [20]. Hwang et al. study on 1229 men aged 25–60 years without diabetes at baseline, of which 90 developed type 2 diabetes during mean follow-up of 8.4 years. Baseline total osteocalcin was inversely associated with HOMA-IR in cross-sectional analysis, but was not associated with incident type 2 diabetes in longitudinal analysis [26]. A cross-sectional study by Weiler et al. on Canadian females showed that insulin resistance (HOMA-IR) increased significantly with the decrease in serum osteocalcin ($r = -0.21$, $p <$ 0.0001) [27].

The mice models have proven that serum osteocalcin increases beta cell function [2]. Apart from animal studies, there are clinical studies in humans which had seen association between serum osteocalcin and HOMA-β. A cross-sectional analysis by Hwang et al. on 252 Korean diabetic subjects showed that the beta cell function (HOMA-β) improved significantly ($p < 0.001$) as the serum osteocalcin level increased [19]. Kanazawa et al. study on Japanese diabetic individuals who were not on anti-diabetic drugs had significant increase in beta cell function ($p < 0.05$) with increase in serum osteocalcin levels [28]. But, Wang et al. study on Chinese diabetic individuals found no association between HOMA-β and osteocalcin [29]. In our study, the serum osteocalcin was not associated with better beta cell function (HOMA-β).

To conclude, in subjects with T2DM, serum osteocalcin decreases with increase in the duration of the diabetes and insulin resistance, and glycated hemoglobin (HbA1c) reduces significantly with increase in the serum osteocalcin levels. The findings suggest that the serum osteocalcin has definite association with glucose metabolism in T2DM.

Limitations

- As this was a cross-sectional study, we do not know the exact association with the parameters of glucose metabolism on longitudinal basis.
- Our sample size is only 120, a larger sample size would have yielded better results.
- Bone mineral densitometry was not done in all subjects to rule out osteoporosis conclusively.
- Age significantly affects bone turnover and osteocalcin. Mean age of our study population does not represent this age variation.

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Declarations

Ethics approval Ethical clearance for the research project was obtained from the Institutional Ethics Committee (IEC) of KMC & Kasturba Hospital, Manipal (IEC: 737/2017) and was registered in CTRI (Clinical Trial Registry-India) (CTRI/2019/01/017181).

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Could the PON1 phenotype play a key role in insulin resistance?

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Abstract

Aim/objectives Recent studies have shown that Paraoxonase (PON1) enzyme plays a possible role in insulin synthesis by stimulating insulin release from β-cells of the pancreas as well as its anti-atherosclerotic property. In our study, we revealed the relationship between phenotypes of the PON1 enzyme and insulin resistance (IR) and impaired fasting glucose (IFG).

Materials and methods A cohort of 71 IR, 63 IFG, and 68 healthy individuals was examined in this study. The phenotypic distribution was demonstrated by studying PON1 enzyme's Paraoxonase (POase) and Arylesterase (AREase) activity with automated measurement kits.

Results By measuring the ratio of POase activity to AREase activity, 3 different phenotypes (QQ (Risky or Bad Phenotype), QR (Notre Phenotype), and RR (Good Phenotype)) were discovered. The results showed that IR and IFG individuals had riskier phenotypes compared to the control group. In addition, individuals with bad phenotypes were found to be 1.85 and 2.16 times more likely to get IR and IFG, respectively. Both groups were found to be four times more likely to be affected by the bad phenotype (odds ratio: 3.69 and 4.47 respectively).

Conclusion In this present study, the relationship between PON1 enzyme phenotypes and IR was evaluated for the first time in this field. Decreased PON1 activity and poor phenotype may also increase the development of hyperglycemia or diabetes mellitus (DM) due to IR and IFG. It may also predispose to diseases such as atherosclerosis. Therefore, we think that further investigations to explain the possible mechanisms underlying the relationship between PON1 phenotypes, IR and IFG will be useful in the early diagnosis and prevention of *prediabetes.*

Keywords Prediabetes · Paraoxonase · Arylesterase activity · Phenotype · Insulin resistance.

Introduction

Prediabetes occurs when the fasting plasma glucose concentration approaches the lower limit used for the diagnosis of diabetes. This process starts with β-cells of pancreas functional disorders, progressing with insulin resistance and glucose changes [1]. There are two conditions for prediabetes: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG is associated with increased gluconeogenesis development while IGT with peripheral insulin resistance. In cases of simultaneous formation of both, hepatic insulin resistance and increased gluconeogenesis occur [2]. Clinical studies state that individuals with prediabetes may have a high risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases. According to Groop et al., T2DM is a multifaceted disease associated with genetic and clinical heterogeneity [3]. It has been determined that diabetes is associated with macro and microvascular complications, with low PON 1 activity in T2DM patients [4]. Therefore, in prediabetes cases, early diagnosis has great importance for the treatment of these patients [5].

The development of T2DM begins with insulin resistance. This resistance is a condition in which the physiological response to the normal effects of insulin is impaired. In other words, IR can be defined as a subnormal biological response to insulin at a certain concentration or the impairment of the expected effect of insulin on glucose homeostasis, and a lack of response to insulin [6–8]. Insulin resistance is biological

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unresponsiveness to insulin hormones, which occurs with genetic factors, inactivity, obesity, and advancing age [6–9].

Paraoxonase (PON1) is a 45 kDa glycoprotein and shows its enzymatic effect (Paraoxonase, arylesterase, diazonase, etc.) according to the related substrates (paraoxon, phenylacetate, diazoxin, etc.). PON1 hydrolyzes aromatic carboxylic acid esters and is synthesized by the liver and is tightly linked to HDL. This protein prevents oxidation of LDL by hydrolyzing lipid hydroperoxides in vivo. HDL-bonded PON1 slows down the oxidation of LDL and PON1 is a major antiatherosclerotic component of HDL [10]. Therefore, many studies have shown that HDL reduces lipid peroxides by these enzymatic mechanisms during the accumulation of lipid peroxides [11–16]. There are two amino acid polymorphisms in PON1 activity. One of them consists of the substitution of the amino acids methionine and leucine (M/L) at position 55; the other by the substitution of the amino acids arginine and glutamine at position 192 [R/Q]. Three different phenotypes were obtained by the ratio of Paraoxonase (POase) and Arylesterase (AREase) activity of PON1. These phenotypes, which can be easily distinguished on the graph (Fig. 1), are especially due to difference in POase activity. Those with low activity are classified as risky or bad phenotype (QQ); those with medium activity as moderate phenotype (QR), and those with high activity as good phenotype (RR) [17, 18].

Since IR and IFG pose a risk for diabetes mellitus-related diseases and cause various complications in the chronic period, early diagnosis and correct treatment of patients would benefit society. Accordingly, it is obvious that any scientific study to be conducted on them would have great importance. Studies related to IFG, IR, and PON1 enzymes are limited. Therefore, this study can contribute to the literature. In our study, both paroxanase and arylesterase activity of PON1 enzyme in individuals with IFG and IR were studied and the phenotype they had was investigated with these data. For this purpose, the possible role of the PON1 enzyme was investigated with data obtained from the control and patient groups.

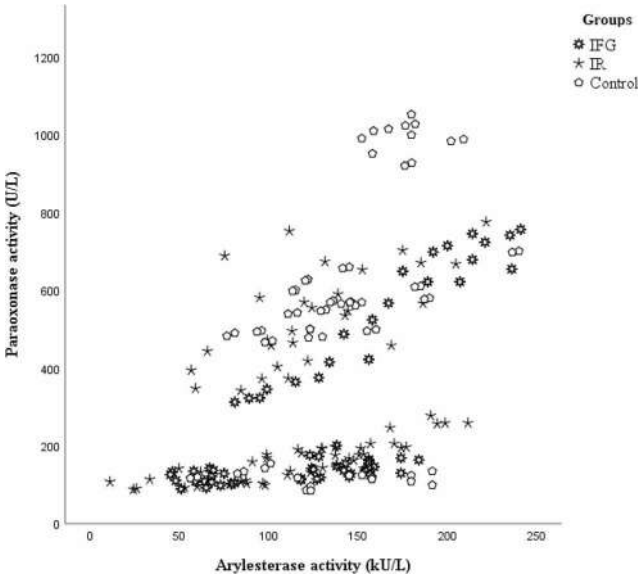

Fig. 1 Paroxanase and arylesterase activities of groups

Material and method

Ethical statement and clinical information

After blood samples were taken from the patients who applied to the Bezmialem Vakıf University Health Research and Application Center Endocrine Polyclinic, their weight, height, and body mass index (BMI) were recorded.

Study design and blood tests

Considering the World Health Organization (WHO) diabetes diagnosis criteria and statistical power analysis (5% type 1 error level and 80% power level), 71 individuals (31 women and 40 men) IR, 63 individuals (28 women and 35 men) IFG, and 68 individuals (30 females and 38 males) were included in the study as a control group. Samples were collected between August and October 2019.

After 8–10 h of fasting, blood was drawn into Hemogram and Gel tubes. HbA1c was studied from hemogram tubes. After the blood samples in the gel tubes were centrifuged at 3600 rpm for 6 min, glucose, HDL-cholesterol, LDL-cholesterol, triglyceride, and insulin were studied in an autoanalyzer device (Abbott Architect Illinois, USA). Patients with blood glucose levels below 126 mg/dL were divided into groups by glucose tolerance test.

The HOMA-IR measurement method, which was first described by Matthews and her colleagues, is made with the help of mathematical data that allows quantitative measurement of insulin resistance. Unlike other tests, it determines basal insulin resistance. With the HOMA formula, insulin resistance and β-cell function (HOMA-β) are processed and are calculated [19]. The HOMA index and the insulin resistance index values are directly proportional, and insulin resistance also increases in conditions where the HOMA level is high. Considering the prevalence in the Turkish population, it has been reported that insulin resistance occurs at levels above 2.4–2.7 HOMA values [20]. The HOMA-IR index is calculated in mg/dL by multiplying the fasting plasma glucose value with the insulin value and dividing the result by 405. The HOMA-IR was calculated according to the formula: (fasting glucose level (nmol/L) x fasting insulin level (microU/L) /22.5). Scientist Eriksson described the insulin resistance measurement as an "early period predictor" in the Type 2 DM process [21].

Those with a fasting glucose lower than 110 mg/dL or less than 110 mg/dL in the 2nd hour after loading 75 g OGTT and HOMA-IR < 2.5 were accepted as the control group. Those with a fasting glucose between 110 and 125 mg/dL and those with a glucose between 110 and 140 mg/dL at 2 h after 75 g OGTT loading and those with The HOMA-IR < 2.5 were included in the impaired fasting glucose group (IFG (+) IR (−)). In addition, those with a fasting glucose between 110 and 125 mg/dL and those with a glucose between 110 and 140 mg/dL at the 2nd hour after 75 g OGTT loading and HOMA-IR > 2.5 were included in the IFG combining IR group (IFG (+) IR (+)). Thus, the impaired fasting glucose group and the groups with insulin resistance were completely separated from each other. HOMA-IR calculation was obtained by dividing the product of fasting blood glucose (FBG) and insulin by the number 405. In addition, some of the samples were transferred to Eppendorf tubes and stored at −80. After the samples reached the planned number, the tubes were dissolved, and enzyme activities were studied.

Enzyme activities

Paraoxonase (POase) and Arylesterase (AREase) activity was studied with commercially available Rel Assay Diagnostic kits (Rel Assay Diagnostics, Gaziantep, TURKEY). POase activity was determined by the kinetic measurement of the p-nitrophenol product at 412 nm, which is formed in the basic environment where the enzyme's substrate paraoxon and its cofactor calcium are present at 412 nm. The result was calculated using the molar absorption coefficient of the p-nitrophenol molecule (18,290 M–1 cm^{-1}) and was defined as Unite/L.

AREase activity was measured by the increase in the concentration of the phenol product formed in the presence of phenylacetate, the substrate of the enzyme. Enzymatic activity was calculated using the molar absorption coefficient of the produced phenol (1310 M–1 cm¯1). It was determined by defining each 1 μmol of phenol produced by measurement at 340 nm as 1 Unite/L [22].

PON1 enzyme polymorphism was determined according to the distribution of POase and AREase activities. POase activity was placed on the Y-axis and AREase activity was placed on the X-axis and the groups were determined with 3 different polymorphisms. Three phenotypes were identified as homozygous low activity AA (QQ), heterozygous medium activity AB (QR), and homozygous high activity BB (RR).

Exclusion criteria from the study

Patients who used medication for any disease such as diabetes mellitus, cardiovascular, neurological, liver, rheumatoid arthritis, anemia, and kidney disease were excluded from the study. Individuals with cancer or a history of cancer, those diagnosed with hepatitis and blood pressure, and those using serum lipid lowering, antipsychotic, insulin, and antioxidant drugs were not included in the study. Pregnant individuals and women with a history of gestational diabetes and individuals who are not suitable for the age range, children, and infants were not included.

Statistical analysis

The data obtained from the study were analyzed using IBM SPSS Statistics v.27.0 package program. To analyze the relationship between the dependent and independent variables, a logistic regression method was used. The differences between independent variables were analyzed by independent sample *t* test, and the relationship between variables was analyzed with Pearson correlation coefficient. The mean and standard deviation were calculated as descriptive statistics. Since variance homogeneity in POase and AREase activities was not fully ensured, a nonparametric Mann-Whitney *U* test was also applied, and the results were similar to those obtained from parametric tests. Statistically, $p < 0.05$ values were considered significant. The relationship between the groups was examined using the Chi-square test. As a result of the chi-square analysis, good phenotype, and bad phenotype risk analysis (risk estimate and odds ratio) were performed, and the results were presented (Tables 2 and 3). In addition, Phi and Cramer *V* values were also added to the table to reveal the effect values of the significance level.

Results

Demographic, clinical, and laboratory findings of participated individuals are shown in Table 1. The data on age, sex, and BMI displayed not significant difference between the 3 groups ($p > 0.05$). Fasting glucose levels in peripheral bloods of IFG (+) IR (−) and IFG (+) IR (+) patients have been found to be significantly higher compared to controls ($p < 0.05$). In both groups, HbA1c, LDL, total cholesterol, and triglyceride were significantly higher compared to the control ($p < 0.05$). IFG (+) IR (−) and IFG (+) IR (+) patients' HDL values were lower than the control groups. PONase and AREase activities were significantly lower in both groups when compared with the control. There were nonsignificant correlations between Paraoxonase and lipid profiles (HDL, LDL, and total cholesterol) ($p > 0.05$) (Table 1). Paraoxonase and arylesterase activities of groups and phenotypic distributions of groups were given in Fig. 1 and Table 2, respectively. Since the overall incidence of BB (RR) polymorphisms in populations is very low, BB (RR) and AB (QR) polymorphisms were used together to represent moderate activity in the risk analysis

Table 1 Demographic clinical and laboratory findings

Parameters	IFG(+) IR(−) (*N*=63)	IFG(+) IR(+) (*N*=71)	Control (*N*=68)	*p*
Age	49.53 ± 10.93	45.32 ± 12.73	44.21 ± 14.34	ns
BMI (kg/m^2)	22.3 ± 1.1	23.7 ± 1.4	21.5 ± 0.9	ns
Glucose (mg/dL)	109.74 ± 9.06 [a]	112.93 ± 10.41 [a]	90.91 ± 4.46 [b]	< 0.01
HbA1c (%)	5.46 ± 0.28 [a]	5.72 ± 0.41 [a]	5.23 ± 0.24 [b]	< 0.05
Insulin (μIU/mL)	5.82 ± 2.47 [b]	13.75 ± 3.82 [a]	6.28 ± 3.04 [b]	< 0.05
LDL (mg/dL)	133.82 ± 39.46 [a]	130.20 ± 30.74 [a]	105.61 ± 36.84 [b]	< 0.05
Triglyceride (mg/dL)	128.71 ± 48.64 [b]	142.46 ± 63.48 [a]	120.92 ± 66.62 [b]	< 0.05
HDL (mg/dL)	51.17 ± 11.3 [a]	44.91 ± 9.34 [a]	56.68 ± 16.61 [b]	< 0.05
Total Cholesterol (mg/dL)	205.15 ± 53.83 [a]	203.06 ± 49.65 [a]	169.22 ± 42.99 [b]	< 0.05
Paraoxonase activity (U/L)	276.48 ± 220.4 [a]	307.96 ± 204.2 [b]	505.30 ± 301.4 [c]	< 0.01
Arylesterase activity (kU/L)	131.49 ± 52.75 [a]	120.65 ± 47.99 [a]	142.29 ± 38.82 [b]	< 0.05

a, b, c Within rows. Means followed by the same letter are not significantly different according to ($p < 0.05$)

$p > 0.05$ shown as ns (not significant)

calculation. Thus, individuals were divided into 2 groups as bad polymorphism (QQ) and good polymorphism (QR, RR) (Table 2). In the chi-square analysis, the frequency of IFG (+) IR (−) and IFG (+) IR (+) was significantly higher in patients with poor phenotype. As seen in Table 3, the risk of developing IFG (+) IR (−) with bad phenotypes was 2.16 times higher than those with good phenotype (Relative risk); in other words, those with IFG (+) IR (−) had a bad phenotype. The probability of being affected was determined as 4.47 times higher (Odds ratio). However, the risk of getting IFG (+) IR (+) was 1.85 times higher than those with good phenotype (Relative risk). In other words, those caught IFG (+) IR (+) were found to be 3.69 times more likely to be affected by the bad phenotype (Odds ratio) (Table 3).

Discussion

In our current study, PONase and AREase activity was significantly lower in individuals with IFG (+) IR (−) compared to controls. We found that individuals with bad phenotypes had 2.16 times higher risk of getting IFG (+) IR (−) than normal individuals. In addition, individuals with IFG (+) IR (−) were found to be 4.47 times more likely to be affected by the bad phenotype. PONase activity has a relationship with IFG (+) IR (−) as well as IFG (+) IR (+). Although there are a few activity studies on insulin resistance and impaired fasting glucose, the phenotypic study was evaluated for the first time in this study. We speculate that having a bad phenotype in individuals with IFG (+) IR (+) may bring along lipid metabolism disorders. However, because of metabolic and endocrine disorders, it sets the ground for possible future coronary artery disease. Therefore, low PON1 enzyme activity may become an important criterion in the diagnosis of such diseases. In line with this theoretical and applicable information, patients with the PON1 phenotype may have a higher risk of developing insulin resistance or impaired fasting glucose. The probability of observing, diagnosing, and treating many health problems such as DM and coronary artery disease in advance increases.

The paraoxonase gene family has 3 members, namely PON1, PON2, and PON3. These are located on the long arm of human chromosome 7 between q-21.3 and q-22.1. It is believed that the product of PON1 and PON3 genes is in

Table 2 Phenotypic distributions of groups

Parameters	Control	IFG(+) IR(−)	IFG(+) IR(+)	*p*
Bad phenotype	20[b]	41[a]	43[a]	< 0.001
	% 29	% 65	% 61	
Good phenotype	48[b]	22[a]	28[a]	< 0.001
	% 71	% 35	% 39	
Total	68	63	71	

a, b, c Within rows. Means followed by the same letter are not significantly different according to ($p < 0.05$)

$p > 0.05$ shown as ns (not significant)

Table 3 Relative risk and odds ratios

Parameters	IFG(+) IR(−)	IFG(+) IR(+)	*p*
Odds ratio	4.47	3.69	< 0.001
Relative risk	2.16	1.85	< 0.001
Phi and Cramers V	0.357	0.323	

The *p* value obtained as a result of the control group comparison is indicated

IFG(+) IR(−): individuals who got impaired fasting glucose but not insulin resistance

IFG(+) IR(+): individuals who got both impaired fasting glucose and insulin resistance

plasma, while PON2 is in the cell. PON2 and PON3 are not understood as well as PON1 due to the lack of research on them. In past studies with PON1, the relationship between human serum capacity, hydrolysis of xenobiotics, and atherosclerosis has been investigated [11, 15, 17, 23–25]. The phenotypic distribution in humans causes the formation of a polymorphism. With paraoxonase enzyme polymorphism, the PON1 192R isoform hydrolyzes the paraoxon faster than the PON1 192Q form, making the elimination of Ox-LDL formed in the body more effective. Individuals who have poor PON1 phenotype with low activity can get coronary artery disease faster [15, 17, 25]. Paraoxonase activity may also closely be related to dietary intake. There are studies reporting that fruit, tea, and butter in the diet increase Paraoxonase activity and correlate with protein, Monounsaturated, Polyunsaturated, Vitamin E, flavonoids, and Quercetin [26]. Paraoxon hydrolytic activity of PON1192RR and PON155LL purified from high level PON1 is the highest, while this activity is the lowest in PON1192QQ and PON155MM. The paraoxon hydrolysis activity of the protein encoded by the R allele is eight times higher than the Q allele. The intermediate step of the activity is homozygous [27].

It is clear that paraoxonase activity may be associated with many diseases or conditions in the body, as well as with cardiovascular diseases and diet. Paraoxonase activity has been found to be low in patients who develop diseases known to be associated with coronary artery disease, such as obesity, DM, hypercholesterolemia, and renal failure, serum diabetic retinopathy, and hypertension [15, 16, 28]. Recently, it has been shown that the expression of human PON1 can prevent the development of diabetes in mice through its antioxidant properties and stimulation of β-cell of pancreas insulin release, suggesting a possible role for PON1 in insulin biosynthesis. PON1 may be a powerful antioxidant and antidiabetic enzyme [29].

Increasing the fat ratio in the body causes insulin resistance leading to obesity. Accordingly, central obesity, dyslipidemia, and genetic factors may cause the onset and development of insulin resistance [7]. Similar to the above studies, the PON1 activity of individuals with insulin resistance was studied in our current study, and the phenotype was investigated with the obtained data. It was observed that PONase and AREase activity was significantly lower in individuals with insulin resistance. In addition, individuals with bad phenotypes were found to have 1.85 times higher risk of getting IR than normal individuals. However, individuals with IR were found to be 3.69 times more likely to be affected by the bad phenotype (odds ratio). Considering these data obtained from previous studies, there may be a strong relationship between low PON1 activity and IR. However, it can be stated that PON1 plays a protective role in IR, as in many diseases, especially coronary diseases.

According to the 2019 WHO guidelines, IFG was evaluated as an impaired step in carbohydrate metabolism [30]. A fasting blood glucose level of 110–125 mg/dL (6.1 to 6.9 mmol/L) is defined as impaired fasting glucose [30]. IFG, which is also considered as an intermediate metabolic disorder, is stated to be an important risk factor in terms of diabetes and/or cardiovascular diseases [31]. Lu et al. conducted a study on 284 patients, supporting our findings. According to this study, they found that PON1 activity was significantly lower in patients with coronary heart diseases and IFG compared to the control group. The activity and structure of PON1 can be changed during glucose and/or lipid oxidation process. There are components that inhibit PON1 activity, such as advanced glycation end products in patients with DM. However, PON1 can decrease its activity by glycosylation itself. In the same study, altering the physicochemical properties of HDL may affect PON1 activity in HDL metabolism, and decreased HDL size and unesterified cholesterol accumulation in the HDL particle, increasing PON1 release and impairing its capacity to stabilize enzyme activity [32].

The main limitation of the current study is the lack of sufficient IGT sample size for significant statistical analysis to compare PONase and AREase activity and therefore, their effect on above-mentioned diseases could not be compared. Additionally, the number of studies which dealt with PONase and AREase activity and phenotype distribution was not sufficient enough to compare with our current study.

As a result, observing changes in PON1 activity may contribute to the prediction of diffuse, severe, or multiple disease lesions in patients with IR, IFG, or complications. The decrease in PON1 activities may increase the development of hyperglycemia, DM, and atherosclerosis due to IR and IFG. Therefore, it would be useful to conduct further research to explain possible mechanisms underlying the relationship between the PON1 phenotype, IR, and IFG. Further clinical, molecular, and biochemical studies are required to reveal all possible functions of PON1.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This study was carried out with the permission no 06/08/2019–13,038 obtained from Bezmialem Vakif University Non-Interventional Research Ethics Committee.

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Importance of work
Detailed Budget sought along with full justification/ proposed utilization, of funding sought from RSSDI

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