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EDITORIAL

Diabetic kidney disease and diabetic retinopathy: the ominous duo

Vijay Viswanathan [1]

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Diabetic kidney disease (DKD) and diabetic retinopathy (DR) are two feared complications of diabetes. The article by Dash et al., in this journal, "Diabetic retinopathy and its association with low glomerular filtration rate: a cross sectional analysis of diabetes patients of community clinics across India", looks at the association between these two microvascular complications [1].

In this retrospective study of 1547 people with type 2 diabetes mellitus (T2DM), they looked at the association between DKD and DR in 443 people. The prevalence of DR was found to be more in people with lower estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2. There was also a significant correlation between low levels of eGFR and DR [1].

The expenditures on hospitalisation for people with diabetes and DKD in India are considerably higher than in those without any complication [2]. In a 12-year observational study in India, Viswanathan et al. found that among 152 people who had normoalbuminuria at baseline, the presence of diabetic retinopathy showed a significant association with the development of macroalbuminuria [3]. In another study by the author, comparing people with proteinuria and those without proteinuria, it was observed that diabetic retinopathy was present in 100% of proteinuric patients vs 24% in the non-proteinuric group [4].

The author also studied the renal-retinal relationship in people with T2DM in India [5]. The mean decline in renal function worsened significantly as the severity of DR increased. The mortality rate was higher in people with both DKD and DR.

In a recent study done in a tertiary care diabetes centre in South India, the effect of DKD on the development of new-onset DR and sight-threatening diabetic retinopathy (STDR) was studied [6]. Higher serum creatinine, low eGFR and the presence of macroalbuminuria were associated with increased risk of progression to STDR [6].

From the above-mentioned discussion, it is very evident that in people with DM, the presence of DR is associated with worsening kidney function. It is also seen that in people with declining kidney function, the risk of severe DR is also increased. The relationship between the degree of diabetic retinopathy and the severity of glomerular lesions in people with T2DM may not always show concordance.

Discordance between DKD and DR occurs often. Some people with DR do not have any evidence of DKD. Discordance between these two conditions is believed to be due to some differences in the pathogenesis of these two conditions. A recent population-based study on multi-ethnic Asian adults found that those patients with concordance of both DKD and DR had a higher risk of all-cause and CV mortality [7].

The general concept is that all people with DKD will exhibit some degree of DR. The rapid onset or progression of proteinuria, lack of DR, presence of hematuria and active urine sedimentation suggest a non-diabetic etiology and warrant a kidney biopsy. It is also known that there exists an entity called normoalbuminuric DKD where chronic kidney disease is present without any albuminuria [8].

Therefore, it is mandatory to closely follow the kidney function in people with diabetes with both estimation of albumin in the urine and estimation of eGFR. The authors had shown that in India the CKD Epi [Sr Cr] is a good formula to determine the eGFR [9, 10]. It is also important to motivate people with diabetes to have a regular eye test to diagnose common problems like cataract, glaucoma and DR.

Therefore in conclusion, every physician dealing with people with diabetes should educate their patients about the importance of regular screening for DR to prevent blindness and estimation of the urine albumin concentration by a simple urine albumin/creatinine ratio and calculation of the eGFR.

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REVIEW ARTICLE

COVID-19 and type 1 diabetes: dealing with the difficult duo

Subhankar Chowdhury[1] · Soumik Goswami[2]

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Abstract

Background Coronavirus disease 2019 (COVID-19) has aroused global health concerns, particularly in relation to diabetes where it has been associated with poorer outcomes. The bulk of the evolving evidence in diabetes and COVID-19 relates to type 2 diabetes (T2D). Since there are a significant number of patients with type 1 diabetes (T1D) with unique concerns and challenges during the ongoing COVID-19 pandemic, we reviewed existing literature, relevant websites, and related guidelines to form this narrative review to help address key questions in this area.

Methods We systematically searched the PubMed database up to May 31, 2020, and retrieved all the articles published on T1D and COVID-19.

Results We found 18 relevant articles, each of which carried a part of the evidence regarding the risk of contracting COVID-19 in patients with T1D, effect of COVID-19 on development of T1D, outcomes in T1D with COVID-19, and special management issues in T1D in the light of COVID-19. These have been documented in the present review.

Conclusion COVID-19 with T1D presents special challenges. While the available evidence does shed some light, we need more evidence to deal with this difficult duo.

Keywords COVID-19 · SARS-CoV-2 · Type 1 diabetes · Diabetic ketoacidosis

Coronavirus disease 2019 (COVID-19) epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in December 2019 and has progressed rapidly into a pandemic since the first quarter of 2020 [1]. COVID-19 is commonly characterised by fever, cough, fatigue, shortness of breath, pneumonia, and other respiratory tract symptoms and may even progress to death in some [2]. Patients with older age, hypertension, male gender, heart disease, cerebrovascular disease, kidney disease, hyperglycemia, or history of smoking have been shown to have a higher risk of developing more severe disease and subsequent mortality [3–6]. There have been several publications from the global scientific community on COVID-!9 in type 2 diabetes (T2D) but markedly fewer looking at type 1 diabetes (T1D). T1D constitutes about 5% of all diagnosed cases of diabetes and its global incidence is increasing at about 3% every year [7]. Given the global burden of T1D and unique challenges in treating T1D (more so in developing nations like India), this narrative review attempts to address key questions regarding COVID-19 and T1D. We systematically searched the PubMed database up to May 31, 2020, and retrieved 18 articles published on T1D and COVID-19 besides looking at relevant websites and related guidelines to form this review.

Risk of contracting COVID-19 in patients with T1D

Diabetes patients have an increased risk of infection compared with the general population and the risk is even greater in those with T1D than in T2D [8]. These include bacterial, viral, and fungal infections of the respiratory tract, urinary tract, gastrointestinal system (including liver), skin and soft tissue, head and neck, and other systemic infections (e.g. HIV) [9]. This increased risk of infection is due to hyperglycemia-induced immune dysfunction (damage to the neutrophil function, depression of the antioxidant system, and humoral immunity), micro- and macro-angiopathies, and greater requirement of medical interventions in these patients [9].

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Interestingly, in reports from Italy and China, COVID-19 cases with type 1 diabetes were apparently not reported despite a large number of people being infected and hospitalised [10–12]. Possible explanations for the same include a younger age of T1D patients, lower prevalence of T1D, and overexpression of CD8+ T lymphocytes in T1D which might play a protective role (CD8+ T lymphocytes show an increased apoptosis leading to lymphocytopenia in SARS-COV2 infection) [13]. However, population cohort studies covering all individuals registered with a general practice in England show that T1D patients do contract COVID-19 infection requiring hospitalisation in some [14, 15]. Presently, as testing for COVID-19 is still limited and as there could be many asymptomatic individuals with the infection, it remains unclear whether T1DM patients are more likely or less likely to contract COVID-19. A study in regions with a high prevalence of T1D (e.g. Scandinavian region) looking at the prevalence of COVID-19 infection with widespread community screening in those with and without T1D could possibly provide an answer. Since it is well established that uncontrolled hyperglycemia impairs immune function in all forms of diabetes, it would be logical to presume that T1D, particularly if not well controlled, could have an increased risk of infection and intensifying glycemic control could serve as a means of primary prevention [16, 17].

Effect of COVID-19 on development of T1D

Viral infections are well known to be associated with the development of pancreatic autoantibodies leading to T1D in genetically predisposed individuals and coronaviruses were identified as one of the incriminating pathogens in the TEDDY study [18, 19]. Viral infections trigger autoimmune insulitis and pancreatic β-cell destruction through several mechanisms—virus amplification cycle and/or circulating viral antigens may directly damage β-cells and also lead to the release of sequestered islet antigens which are presented by overexpressed major histocompatibility complex class I proteins to the immune system, increasing the risk of autoantibody generation. Viral epitopes sharing homology to autoantigens could lead to cross-reactive antibody production against β-cells (molecular mimicry hypothesis). Also, viral infection leads to cytokine release and T cell activation which could hasten the development of T1D in genetically predisposed individuals [20]. SARS-CoV-2 might also bind to ACE2 in the pancreas and cause pancreatic injury, particularly in severe COVID-19 cases, thereby hastening the development of overt T1D in susceptible individuals [21]. As T1D development has already been related to coronavirus respiratory infections, it is very likely that an increasing incidence of T1DM may be triggered by the present pandemic and appropriately designed studies are necessary in this regard. Till such published evidence becomes available, practitioners have to be on an active lookout for the development of T1D after COVID-19 in predisposed individuals. There is a report of an individual presenting with diabetic ketoacidosis (DKA) as an inaugural feature of T1D where DKA symptoms were masked by COVID-19 symptoms; this is an area where we need to be vigilant as well [22].

COVID-19 and T1D—outcomes

While T2D and its associated comorbidities have established themselves as risk factors for increased hospitalisation, requirement of intensive care, and mortality with COVID-19, early anecdotal reports from global infection hotspots suggested that children with diabetes had a similar disease pattern compared with children without diabetes (less severe manifestations than adults) [23, 24]. On the contrary, a large population cohort study assessing the risk of in-hospital death for individuals registered with a General Practice in England showed that people with T1D had 3·50 (3·15—3·89) odds of dying in hospital with COVID-19 compared with those without diabetes which was attenuated to 2·86 when also adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure [14]. However, this study also found a very low absolute risk of in-hospital death for people with diabetes under 40 years of age implying that age was a stronger risk influencer than diabetes status [14]. Another study from England using national diabetes and mortality data showed that the adjusted hazard ratio (HR) for mortality in COVID-!9 with T1D of HbA1c > 10% compared with HbA1c 6.5–7% was 2·19 [15]. This study also found a U-shaped relationship between body mass index (BMI) and COVID-19 mortality with HRs for BMI > 40 kg/m^2 compared with 25–29.9 kg/m^2 being 2·15 (1·37–3·36) for T1D [15]. Evidence from these studies coupled with the fact that glycosylation of ACE2 receptors (which is necessary for cell entry of SARS-COV2) can be boosted by hyperglycemia makes a strong case for intensifying glycemic control for improving outcomes in T1D with COVID-19 [25].

Special management issues in T1D in the light of COVID-19

a. *Effect of chloroquine and hydroxychloroquine*: There has been an increase in the use of chloroquine and hydroxychloroquine, both for the prophylaxis and treatment of COVID-19. Both these agents have been reported to cause hypoglycemia in patients with and without diabetes (even in those not on insulin or sulphonylureas) [26, 27]. Chloroquine is postulated to reduce blood glucose (BG) levels by stimulating insulin secretion and also by

activating Akt to stimulate glucose uptake and glycogen synthase [28]. Hydroxychloroquine decreases insulin degradation at the cellular level, increases intracellular insulin accumulation, and stimulates insulin-mediated glucose transport [27]. There is a published report of an individual with T1D on insulin developing hypoglycemia after taking chloroquine prophylaxis while visiting a malaria endemic area following which this patient even maintained euglycemia without insulin for a temporary period [29]. Therefore, patients with T1D who are administered chloroquine or hydroxychloroquine need to be monitored closely for hypoglycemia and their insulin doses adjusted as necessary.

b. *Effect of "lockdown"*: Many countries across the world have imposed "lockdown" measures with restriction of movement and mandatory quarantine of individuals with or at risk of infection. While these measures have been lifted in certain countries, there is a distinct possibility of re-imposition of these measures if a "second wave" of infection appears. Since T1D is known to be greatly affected by alterations in daily routine, there are concerns that "lockdown" can worsen glycemic control in T1D due to restriction of outdoor physical activity, psychological stress on account of lack of physical interaction with acquaintances, irregular sleep pattern, and intake of less healthy diet [30, 31]. However, interestingly, there are several publications which have pointed to the contrary—there was either no deterioration in glycemic control or even improvement in glycemic control in T1D during "lockdown", particularly in those who continued exercising and in those who did not go out for work [32–34]. Possible explanations include greater parental control and absence of school-related stress in children and adolescents, eating every meal at home with regular timing and more consistent and precise carbohydrate counting, and reduction of workplace-related stress. Besides slowing of daily activities which might have helped in glycemic control, patients' apprehension of worsening of COVID19 outcomes could have contributed to improved compliance with physician advice resulting in good BG control. However, these studies have primarily looked at adolescents using a hybrid closed loop system and adults using continuous glucose monitoring with good glycemic control at baseline because of which these findings might not be generalisable to those with poorer control and/or not having access to these new technological tools. Another concern is interruption in the availability of insulin and glucose meter test strips in relatively remote area due to logistic issues associated with the "lockdown". In view of this, patients would be well advised to ensure sufficient stocks of essential medical supplies besides maintaining a regular schedule and staying physically active indoors in the interest of good disease control. Patients should be encouraged to pursue in-home physical activity (e.g. bodyweight exercise, jump rope, online lessons) as it can not only help improve glycemic control but also for psychological well-being, since physical activity reduces stress and anxiety and improves mood and sleep quality [35, 36].

c. *Risk of DKA:* While contracting an illness might increase the risk of development of DKA in those with known T1D, there are reports of delayed diagnosis of new-onset T1D leading to presentation with severe DKA [37]. Fear of contracting COVID-19 in a hospital setting, reduced access to hospital emergency departments due to travel restrictions, and hospital services remaining closed for non-COVID-19-related ailments could be some of the causes for this. Another reason could be delayed diagnosis on the part of doctors who are preoccupied with COVID-19 and might not consider DKA in the differential diagnosis when a patient presents with suspected symptoms either over the telephone or in person. Certain features of DKA overlap with viral illnesses in children and physicians should be on their toes to look out for polyuria, polydipsia, weight loss, Kussmaul's respiration, and a fruity odour in breath.

d. *Prevention of DKA:* T1D patients who are ill should be advised to follow "sick day rules" which are recommended for any stressful situation to reduce the risk of DKA [38]. These include the following:

1. Insulin should never be stopped.
2. The insulin dose may need to be increased and it might be necessary to take additional doses of rapid acting insulin to bring down the BG levels (Table 1).
3. BG levels and ketones (especially if BG > 270 mg/dl) should be checked every 2–4 h. Check for urine ketones with test strips if blood ketone meter is unavailable.
4. Plenty of non-sweet fluids should be taken to avoid dehydration. Liquids for hydration should contain salt and water and not just plain water (chicken soup, homemade lemonade with both salt and sugar, or clear broths), particularly if vomiting or diarrhoea result in ongoing losses. If appetite is decreased or the glucose level is falling below 180 mg/dL, sugar-containing fluids should be considered to decrease the risk of starvation ketosis.
5. Regular meals can be replaced with easily digestible food (rice-lentil broths and sugar-containing fluids) to provide energy and avoid starvation ketosis.
6. When the child is feeling sick or vomiting and ketone levels are negative or low (trace or small) with BG < 180–250 mg/dL, sugar-containing fluids in small amounts (at least 100 mL/h) should be administered to keep BG up.

7. BG should be maintained between 110 and 180 mg/dL in otherwise stable individuals.

In the following situations, T1D patients should promptly get in touch with their treating doctor:

1. When not sure what to do
2. If they vomit repeatedly (not able to hold down any food or drink for more than 6 h)
3. If vomiting persists beyond 2 h (particularly in young children)
4. If BG stays high for more than 24 h
5. If they develop symptoms which could be indicative of their developing diabetic ketoacidosis (nausea, vomiting, abdominal pain, shortness of breath, confusion).
6. If blood ketones remain elevated > 1.5 mmol/L or urine ketones remain large despite extra insulin and hydration
7. In very young children (< 5 years)

e. *Management of DKA:* Intravenous (IV) insulin is the standard of care for DKA but may pose a challenge in present times as it often requires admission to the intensive care unit (ICU). ICU beds may be reserved for or be at full capacity with COVID-19 patients besides ICU admission leading to an inappropriate risk of infection in young people with T1D. In this setting, it may be necessary to manage uncomplicated mild to moderate DKA outside the ICU setting with subcutaneous (SC) insulin [39].

SC rapid acting insulin analogs reach peak effect in 90–120 min and can be used for the treatment of uncomplicated mild to moderate DKA outside the ICU setting [40]. SC regular insulin is an alternative if rapid acting analogs are unavailable. SC rapid acting analogs (lispro/aspart) can be started at a dose of 0.15 U/kg 1 h after the commencement of IV fluid replacement. BG levels should be monitored every 1–2 h to maintain levels of around 200 mg/dL until DKA resolves. SC doses should be injected every 2 h until DKA resolution and the dose can be brought down to 0.1 U/kg if BG continues to decrease by > 90 mg/dL per hour. However, SC insulin may be unsuitable for those with severe dehydration or serious comorbid conditions.

SC regular insulin every 4 h can be used if ph > = 7 at a starting dose of 0.13–0.17 U/kg which can be subsequently increased or decreased stepwise by 10–20% depending on BG values. The dosing frequency can be increased to every 2 h if acidosis does not improve [41, 42].

Basal insulin should be initiated once DKA has resolved and oral intake is tolerated. Once DKA has resolved and the child is able to drink adequately, the remaining volume of calculated fluid and potassium deficit can be administered orally to facilitate early hospital discharge thereby optimising the use of healthcare resources and also reducing the risk of contracting COVID-19. Intramuscular (IM) insulin may be used instead of SC insulin in those with poor tissue perfusion [39].

In individuals with T1D and DKA on continuous glucose monitoring system (CGMS), confirmatory BG monitoring with finger-prick capillary blood glucose should be performed in view of issues with CGMS accuracy in the presence of ketosis and rapidly changing BG levels [39].

f. *Psycho-social issues:* A questionnaire-based Danish cross-sectional study involving 2430 adult diabetes patients of whom one-third had T1D found that those with T1D were more likely to worry about being significantly affected due to diabetes and not being able to manage

Table 1 Additional doses of rapid acting insulin necessary to bring down the BG levels

Ketones		Blood glucose		
Blood (mmol/L)	Urine	> 180–250 mg/dL	250–400 mg/dL	> 400 mg/dL
< 0.6	Negative/trace	Give ordinary bolus	Add + 5% TDD or 0.05 U/kg to ordinary bolus	Add + 10% TDD or 0.1 U/kg to ordinary bolus
0.6–0.9	Trace/small	Add + 5% TDD or + 0.05 U/kg	Add + 5–10% TDD or 0.05-0.1 U/kg	Add + 10% TDD or 0.1 U/kg
1–1.4	Small/moderate	Add +5%-10% TDD or 0.05-0.1 U/kg	Add +10% TDD or 0.1 U/kg	Add +10% TDD or 0.1 U/kg
1.5–2.9	Moderate/large	Add + 5–10% TDD or 0.05–0.1 U/kg	Add + 20% TDD or 0.1–0.2 U/kg	Add + 20% TDD or 0.1 U/kg
> = 3	Large	Add + 10% TDD or 0.1 U/kg	Add + 20% TDD or 0.1-0.2 U/kg	Add + 20% TDD or 0.1 U/kg to ordinary bolus

In children and adolescents with pre-illness low (< 0.7 U/kg/day) or high (> 1 U/kg/day) insulin requirements, consider using the percentage (%) calculation

TDD, total daily dose of insulin

diabetes if infected with COVID-19 compared with those with T2D [43]. Therefore, special attention should be given to those with T1D in order to manage their anxieties by providing proper information, counselling, peer support, and access to support helplines.

g. *Use of technology:* The COVID-19 pandemic has put the spotlight on telemedicine and brought it to the forefront of diabetes management. Telemedicine consultation minimises the risk of virus transmission by maintaining physical distancing thereby alleviating the anxiety of T1D patients and their caregivers. It also avoids the cost, time, and inconvenience of travel and waiting at the reception before consultation thereby increasing time for school or work. However, telemedicine does have its share of limitations including inability to perform a proper physical examination, lack of widespread availability of necessary Internet-related infrastructure in several developing countries, and difficulty to establish rapport and address behavior modification in patients [44, 45].

In settings with access to more advanced technology, remote monitoring of electronic data (CGMS, connected insulin pens, connected insulin pumps) enables physicians and other health-care professionals to intervene timely in patients whose condition is deteriorating based on available metrics which could help improve clinical outcomes [46].

The present COVID-19 pandemic has changed the way we deal with a number of diseases including T1D. Since we are in the midst of a relatively new and dynamic situation with evolving evidence, we need to be cautious and also rely on logical thinking and common sense to deal with the difficult duo of COVID-19 and T1D more effectively.

Authors' contributions Both authors have contributed equally in all aspects.

Compliance with ethical standards

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REVIEW ARTICLE

Managing diabetic foot in times of COVID-19: time to put the best 'foot' forward

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Abstract

Introduction The COVID-19 pandemic has had an unparalleled impact on the socio-economic and healthcare structure of India. Due to our large populations of diabetic patients, who have an increased risk of worse outcomes with COVID-19 infection, it is of utmost public health importance to analyse the relationship between the two. The aim of our review was to analyse the possible relationship between COVID-19 infection and DFUs, which are a fairly common, yet serious complication in diabetic patients, as well as their management, under the given changing circumstances.

Methodology An extensive review of related educational articles was analysed from various databases.

Results The two main pathogenic mechanisms described in COVID-19 infection are a cytokine storm (causing ARDS) as well as an acquired coagulopathy, with widespread thrombosis. DFUs are associated with an underlying peripheral neuropathy, a chronic low-grade inflammatory state and peripheral arterial disease, which lead to chronic non-healing ulcers. Similarities seen in the pathogenic mechanisms of these two conditions make a bidirectional relationship highly plausible.

Conclusion Due to the disruptions in the healthcare system brought on by the COVID-19 pandemic, changes in practice to a telehealth-driven approach, with emphasis on homecare and community clinics, need to be adopted, to ensure best possible care to patients with DFUs, in order to reduce their risk of DFU-related complications and need for hospitalization.

Keywords COVID-19 · Diabetic peripheral neuropathy (DPN) · Diabetic foot ulcers (DFU) · Cytokine storm · Ischemia

Introduction

The novel SARS-CoV-2 virus outbreak, which has developed into an unprecedented global pandemic, has massively impacted human health and economy worldwide. In India, at the time of writing this article, there were nearly 5 lakh infected cases, with more than 15,000 deaths [1], thus resulting in an unparalleled detrimental effect on the socio-economic and healthcare structure of the country.

Although a majority of the patients presenting with COVID-19 have been noted to have mild, self-resolving upper respiratory tract symptoms, with preservation of vital organ functions [2], it is potentially fatal in patients with comorbidities like diabetes, in whom it progresses to an acute respiratory distress syndrome (ARDS), resulting in it being a matter of major public health concern. Worse outcomes have been recorded in patients with comorbid conditions like diabetes mellitus, hypertension, chronic obstructive pulmonary disease, obesity and smoking [3–5].

India has one of the world's largest populations of diabetic patients, with the latter at an increased risk of developing worse outcomes following SARS-CoV-2 infection. Patients with diabetes are generally known to have an increased risk of infections, secondary to impaired immune responses, due to an altered cytokine profile, and T cell and macrophage activation, with poor glycemic control further increasing the risk [5]. In addition, diabetes is closely associated with obesity which adds to the risk of worse outcomes due to the development of a chronic low-grade inflammatory state, due to an abnormal secretion of adipokines and certain cytokines (TNF-α and interferons), that can further blunt antiviral responses [6]. Though the relationship of COVID-19 with diabetes has been extensively evaluated, its specific impact on the diabetic foot remains sparsely studied.

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Diabetic foot and COVID-19: pathogenetic links

Patients with diabetes develop various microvascular and macrovascular complications during their lifetime, of which peripheral neuropathy and diabetic foot ulcers (DFU) cause a significant negative impact on their quality of life. However, DFU still remains a widely under-reported complication, necessitating a thorough understanding of its etiopathogenesis in times of the COVID-19 pandemic.

Exploring the inflammatory link

There has been a growing clinical and experimental evidence to show the presence of chronic low-grade inflammation and elevated levels of inflammatory cytokines IL-1, 6, 18 and TNFα to be involved in the pathogenesis of both diabetic peripheral neuropathy (DPN) [7] and in the development of DFU [8]. Data from animal studies further lend credence to the inflammatory influence on development of DPN, with diabetic mice treated with COX-2 inhibitors showing no neuropathy, as compared with an untreated group [9]. It is due to this complex mechanism of development of DPN that the treatment has proved to be challenging.

Diabetic foot ulcers develop as a consequence of peripheral neuropathy, abnormal foot mechanics, peripheral artery disease and poor wound healing [10], along with reduced blood flow secondary to peripheral arterial disease increasing the risk of secondary infection.

In diabetes, due to an unbalanced response between pro- and anti-inflammatory mediators, wound healing is impaired, leading to the development of chronic non-healing ulcers [11, 12]. Cytokine growth factors like PDGF, FGF, EGF, VEGF, IGF, TGF, etc. are said to be involved. Due to a disequilibrium studied in the levels of these cytokines, newer treatment modalities using various growth factors are being developed for chronic foot ulcers [13]. The three main factors hindering wound healing are peripheral neuropathy, peripheral arterial occlusive disease and superimposed infection. Also, abnormal or reduced expression of growth factors has been described in diabetic foot ulcers [14]. Some cytokines in the inflammatory cascade like IL-6 are considered to have dual effects, usually having been considered a pro-inflammatory cytokine is now being studied in the treatment of DPN, due to associated positive effects like enhanced blood flow, decreased chronic inflammation as well as peripheral nerve fibre regeneration [15].

The disease pathogenesis, as well as development of complications in SARS-CoV-2 infection, is believed to be via a cytokine storm, which is an uncontrolled aberrant systemic inflammatory response brought about by soluble pro-inflammatory chemical mediators produced by effector cells of the immune system [16]. In patients with COVID-19 infection, high blood levels of cytokines and chemokines have been reported, as in a study conducted by Huang et al. [17]. The cytokine storm, and its resultant ARDS, results from the effects of a combination of various molecules, of which interferons, interleukins, chemokines, colony-stimulating factors and TNF-α represent the main components involved in its pathogenesis [18]. Levels of various cytokines like IL-1β, IL-6, IL-7, IL-10, Il-12, IL-13 and IFN-γ have been shown to correlate severity in patients with SARS-CoV-2 infection [19]. In a study done by Jiang et al., chemokine CXCL10 levels proved to be a good prognostication index in patients with COVID-19 [20].

The SARS-CoV-2 virus is believed to infect cells via ACE2 receptors [21] of the respiratory tract, and as a result of which, diabetic patients who are on ACE inhibitors and ARBs have been shown to have an increased expression of ACE2 [22], increasing their risk of severe disease and possible fatality. DPN and chronic foot ulcers, which are influenced by abnormalities in cytokine levels, have similar pathogenic mechanisms as ARDS in SARS-CoV-2 infection, which is mainly brought about by a cytokine storm [16]. Thus, there seems to be a common inflammatory link between the two conditions.

Another unique manifestation of the diabetic foot is Charcot's neuroarthropathy (Charcot's foot). Secondary to the autonomic neuropathy, an increased local blood flow results in excessive bone resorption leading to a reduced bone mineral density. It is also associated with reduced sensation and impaired proprioception. This excessive local inflammation can result in local osteoporosis [23]. Recent studies have explored the central role of the RANKL-OPG pathway in the pathogenesis of Charcot's foot. A reduction in the neurons producing calcitonin gene-related peptide (CGRP) leads to an increase in RANKL with subsequent decline in joint integrity, thus aggravating the disease process [24]. Since the development and progression of Charcot's neuroarthropathy is closely linked with various inflammatory pathways, it is possible that a bidirectional relationship with COVID-19 infection may exist as well.

Exploring the ischemic link

Patients with DFU often have coexisting peripheral arterial disease (PAD) as a macrovascular complication [25]. Due to this, the occurrence of neuroischemic DFUs is on the rise, and timely intervention with revascularization can impact the ulcer progression timeline [26]. This association has been proved in various studies [26–29]. The neuroischemic component of DFUs is not only due to the macrovascular atherosclerosis but also as a result of impaired vasodilation secondary to the neuropathy, and as a result of which, even with correction of large vessel blood flow by successful bypass grafting surgery, the wound may not completely heal, although there may be considerable improvement [27]. This is the rationale behind

all patients with DFUs requiring an Ankle-Brachial Index (ABI) at baseline to quantify the degree of PAD.

Multiple observational studies have also shown an acquired condition, COVID-19-induced coagulopathy, with widespread development of arterial and venous thrombi in various vascular beds and with a multifactorial etiology [30]. Although the cause is still being widely studied, it has been seen to broadly follow Virchow's triad—endothelial damage, procoagulant substances in the circulation and altered blood flow. A study on 4 deceased patients in New Orleans showed small and firm thrombi in sections of the peripheral lung parenchyma, with no large thromboemboli at the hila [31]. In a study on 183 patients in Wuhan, China, D-dimer, fibrin degradation product (FDP) levels and prothrombin time (PT) were seen to have a significant correlation between disease severity [32]. The hypothesized ACE2-mediated entry of SARS-CoV-2 may be the means of endothelial injury and inflammation due to the widescale expression of ACE2 receptors on endothelial cells across various vascular beds [33]. The role of platelets and inflammatory cells like neutrophils in contributing to widespread microvascular thrombosis has been proposed via a mechanism involving neutrophil endothelial traps (NETs) that can activate the coagulation cascade via endothelial damage [30]. These pathophysiological observations have actually led to clinical recommendations for anticoagulation in COVID-19 patients.

Thus, COVID-19 infection has the propensity to worsen the neuro-ischemic component of DFUs. This has been corroborated in studies from Italy where increased occurrence of acute limb ischemia was seen in patients tested positive for COVID-19 [34]. Given the procoagulant nature of COVID-19 infection, it is possible that patients with diabetic foot ulcers, who already have compromised vascular supply, could have worsening of their foot symptoms and can present with acute limb-threatening crisis requiring hospitalization. Such hospitalizations in diabetes patients with COVID-19 may in turn impact their chances of survival, thus setting up a vicious cycle.

Exploring the vitamin D deficiency link

The relationship between vitamin D deficiency, diabetic neuropathy and COVID-19 is another potentially exciting area of future research. Vitamin D deficiency has been associated with diabetes and its complications with lower levels of vitamin D seen in patients with DPN. In a study by Shehab et al., amongst 210 patients with diabetes, significantly lower levels of vitamin D ($p < 0.05$) were seen amongst those with DPN and therefore proved to be an independent risk factor for DPN [35]. Also, reversal of chronic DPN has been shown with vitamin D supplementation in a deficient type 1 diabetes mellitus patient [36]. The pathogenesis of this phenomenon has been linked to deficient nerve growth in vitamin D-deficient conditions [37]. Recent studies have focused on a possible link between COVID-19 and vitamin D deficiency, with suggestions that patients with vitamin D deficiency may have poorer outcomes than those without [38]. Since, vitamin D is involved in the production of antimicrobial substances in the respiratory tract [39], as well as in reducing inflammatory responses, its deficiency may pose an increased risk of worse outcomes with SARS-CoV-2 infection. Due to this possible dual beneficial effect, supplementing vitamin D in diabetic patients with DFUs and COVID-19 needs to be further looked into as a therapeutic modality.

Figure 1 enumerates the pathogenetic links described above.

Management

Diabetic foot ulcers alone are associated with an increased mortality in diabetic patients (nearly 2.5 times) [40], which can be reduced with adequate treatment and follow-up. In the times before the COVID-19 pandemic, wound care largely aimed at healing patient wounds with a combination of judicious antibiotics, adequate dressing and appropriate offloading. Since these require regular hospital visits, the goal of management has shifted focus to preventing development of wound complications and hospitalization in COVID-19 times [41]. In spite of the pandemic-induced disruption of local practices, it is essential that these patients continue receiving appropriate care while minimizing their need to visit the hospital, and the aim of the physician should be to shift focus away from hospital-based care [42]. Based on the International Working Group on the Diabetic Foot (IWGDF) guidelines [43], most patients with diabetic foot disease do not require hospitalization, unless they have severe infection with possible sepsis or require surgical intervention. By triaging patients, most can be managed as outpatients—with homecare, telemedicine appointments where possible and by setting up clinics at other locations outside of the hospital, with assistance as required from multidisciplinary diabetic foot clinics. Due to the increased susceptibility of this patient group to COVID-19, it is important to ensure that they practice social distancing and hand hygiene while visiting the designated diabetes foot clinics. Also, there is a need to emphasize the importance of proper glycemic control, which may be affected by COVID-19-induced restrictions on outdoor exercise activities. The patients also need to be reminded to continue using their offloading devices or special footwear at home, which may be harder during extended periods of lockdown. The importance of continued exercise as well as any other psychological needs should be catered to via telemedicine appointments. Since physicians will not be able to see their patients in person as often, diagnosing infection can be challenging. A thorough history eliciting important aspects of the temporal profile of ulcer development, features of local

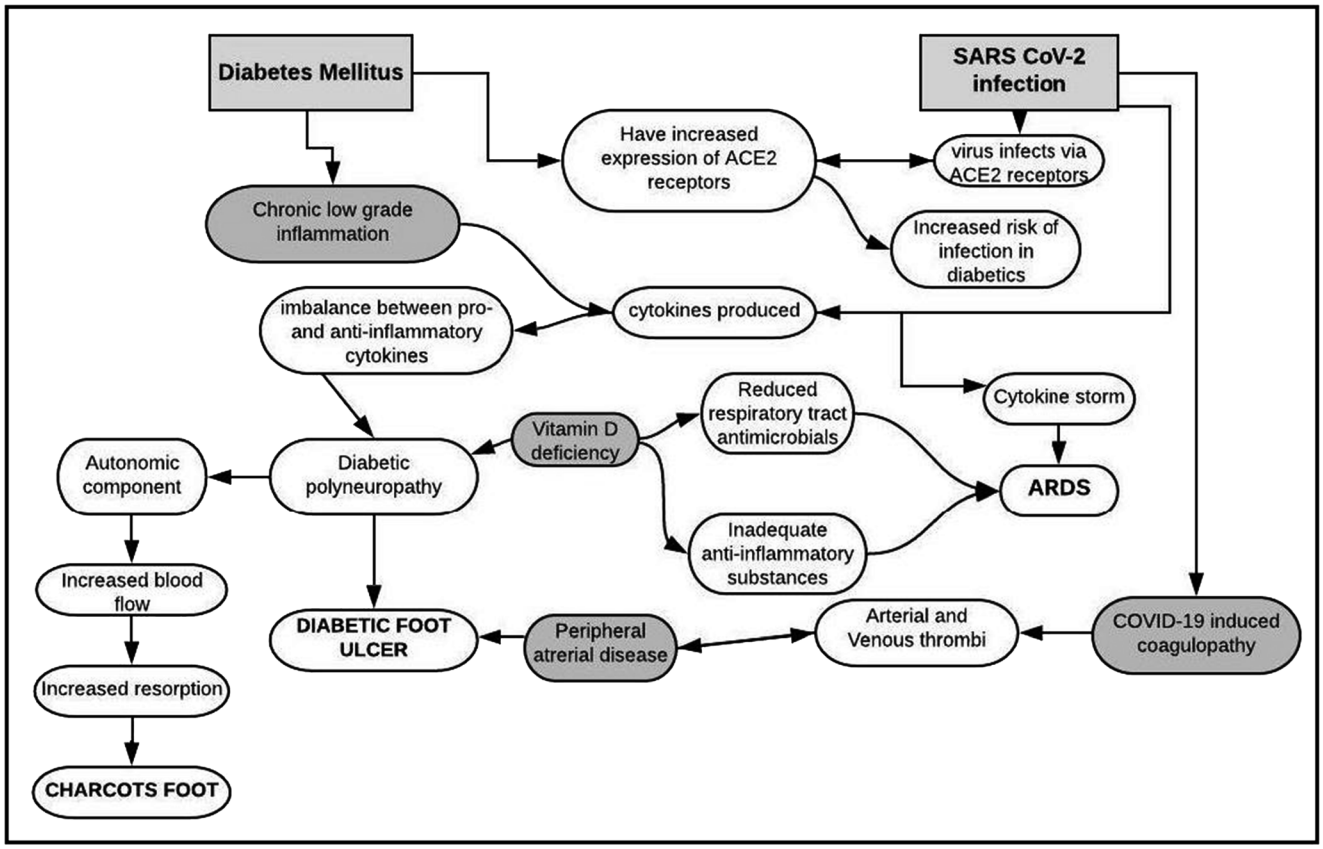

Fig. 1 Pathogenesis: diabetes mellitus, DFUs and COVID-19

and systemic inflammation, wound discharge and glycemic control can help the clinician in this aspect, and antibiotics, if needed, can be prescribed. Patients and their caretakers should be educated on checking the feet for infection or other signs of wound deterioration using handheld mirrors. Education regarding adequate feet hygiene, nail care, appropriate selection of socks and footwear can be imparted over telecommunication and can significantly mitigate the risk of developing DFU. Further, patients should be provided with detailed information on whom to contact and which hospital to go in case any ulcer complication develops.

Effective offloading is known to accelerate ulcer healing and reduce the infection rates and need for hospitalization. Thus, the reduced need for frequent ulcer debridement and dressings can help reduce clinic visits, especially during these times. Although the preferred choice for offloading includes non-removable offloading devices, as patients will not be able to make as many visits to the hospital, the use of removable offloading devices can be promoted. Interestingly, due to the predominantly respiratory symptoms of COVID-19 infection, patients may be less ambulant, and it is possible that this may help with ulcer offloading and accelerate ulcer healing [44]. Emphasis on proper foot care directly reduces their need to visit a healthcare centre and in turn reducing their chance of acquiring COVID infection.

Diagnosis of associated peripheral arterial disease may need to be done over video calls due to the inability to see patients in person. This can be done by analysing certain features like rest pain at the wound while lying flat, tissue loss with new dry or wet gangrene that may mandate urgent surgical debridement or the Buerger test for arterial insufficiency (blanching, numbness and pain at the extremity that develops within a few minutes of limb elevation and reduces when the leg is lowered below horizontal level). If hemodynamic tests are available, critical ischemia will be indicated by ankle systolic pressure < 50 mmHg and toe systolic pressure < 30 mmHg [45]. In patients found to have associated limb-threatening ischemia, the benefit of revascularization to help wound healing and limb salvage outweighs the risks of acquiring COVID-19 infection and is therefore the advisable course of action. The Wound Care Centre Without Walls model of dealing with chronic wound patients during this pandemic is gaining popularity, in order to continue providing wound care to patients untethered to the hospital setting but by using technology and community centred care [41].

Amputations are often required to save the life of affected patients with diabetic foot ulcers that have associated irreversible limb, with severe vascular disease or superimposed ischemic infection. These should be performed after alternative treatments are extensively considered, in view of the high risk

of disease transmission by COVID-19 infected patients during surgery, and should be considered only in patients who will physically be able to tolerate surgery—in a designated hospital, with the required protective equipment. In a patient who presents with severe symptoms of COVID-19, with indications for surgery, the main target should be survival [46]. While optimizing patient care in such scenarios can be challenging, utmost care should also be taken to reduce the threat of infection to the attending surgeons, medical practitioners, nurses and associated healthcare workers.

Based on the guidelines by the American College of Surgeons, guidelines for surgical procedures have been described in Table 1 [41].

COVID-19 and diabetic foot: challenges in the Indian scenario

While most of these guidelines can be applied reasonably well in the western countries, in India, putting many of these guidelines to practice is a challenge due to multiple socio-economic, demographic and healthcare-related diversities across the country. Due to the generally low health-seeking behavior, most patients with diabetic foot ulcers do not realize the need for supervised care, more so amongst those in the lower socio-economic strata, for whom access to proper healthcare is almost always out of reach. This apprehensive behavior may aggravate during pandemics like COVID-19, with initial neglect of a superficial ulcer leading to severe infections and unnecessary hospitalizations, which in turn can spread the pandemic more rapidly. This is where widespread use of telemedicine can be of vital importance. Various government organizations have established telemedicine linkages from many rural areas to hospitals in nearby cities, which in these COVID-19 times can be of immense use, especially for patients with chronic conditions like diabetic foot. Based on the guidelines by the Ministry of Health and Family Welfare (MOHFW) [47], state-registered medical practitioners are eligible to practice using telemedicine which provides physicians with the opportunity to continue managing their patients during this COVID-19 pandemic, except in a few instances where patients need to be seen in person or if hospitalization is required [48]. Wherever possible, the use of a two-way video communication means (like WhatsApp, Facetime, Zoom, etc.) can help the physician in visual evaluation of the wounds and prescribing empirical antibiotics and offloading. Patients can then be asked to send back a photo of their ulcer once a week to the podiatry team, to follow up any improvement or deterioration in their condition. However, telehealth may not suffice in complicated wounds or ischemic foot ulcers and require in-person evaluation. Here also, depending on where the local healthcare system is in the pandemic curve, podiatric nurses and healthcare workers previously caring for patients in the foot care facility can be pivoted to communicating with patients, families and home health services to evaluate the best plan of care, with the goal of keeping the patient at home whenever possible.

Dressing and offloading devices provided by a reliable medical supplier are of paramount importance to sustain home-based care during the pandemic. Dressings in single-dose packages, use of easily available, low-cost materials (like Samadhanam dressing with roller-gauze) [49] and video tutorials on dressing changes are innovative ways that can be adopted in these times.

Table 1 Approach to wound-related surgical procedures in the COVID-19 pandemic

Category	Condition	Management tier
	Lower limb disease with non-salvageable limb (amputation)	3 Do not postpone
Wounds	Amputation for infection/necrosis (TMA, BKA, AKA)	3 Do not postpone
Gangrene	Amputation for necrosis/infection of toes	2b Postpone if possible
Amputation	Deep debridement of surgical wound infection or necrosis	2b Postpone if possible
	Wounds requiring skin grafts	2b Postpone if possible
Venous	Procedures for ulceration secondary to venous disease	2a Consider postponing
	Acute limb ischaemia	3 Do not postpone
	Limb ischaemia, progressive tissue loss, acute limb ischemia, wet gangrene, ascending cellulitis	3 Do not postpone
Peripheral	Fasciotomy for compartment syndrome	3 Do not postpone
Vascular disease	Peripheral vascular disease: chronic limb threatening ischemia, rest pain or tissue loss	2b Postpone if possible
	Peripheral angiograms and endovascular therapy for claudication	2b Postpone if possible
	Surgical procedures for claudication	1 Postpone

TMA Transmetatarsal amputation, *BKA* below-knee amputation, *AKA* above-knee amputation

Adapted from the 'Wound Center Without Walls: The New Model of Providing Care During the COVID-19 Pandemic'

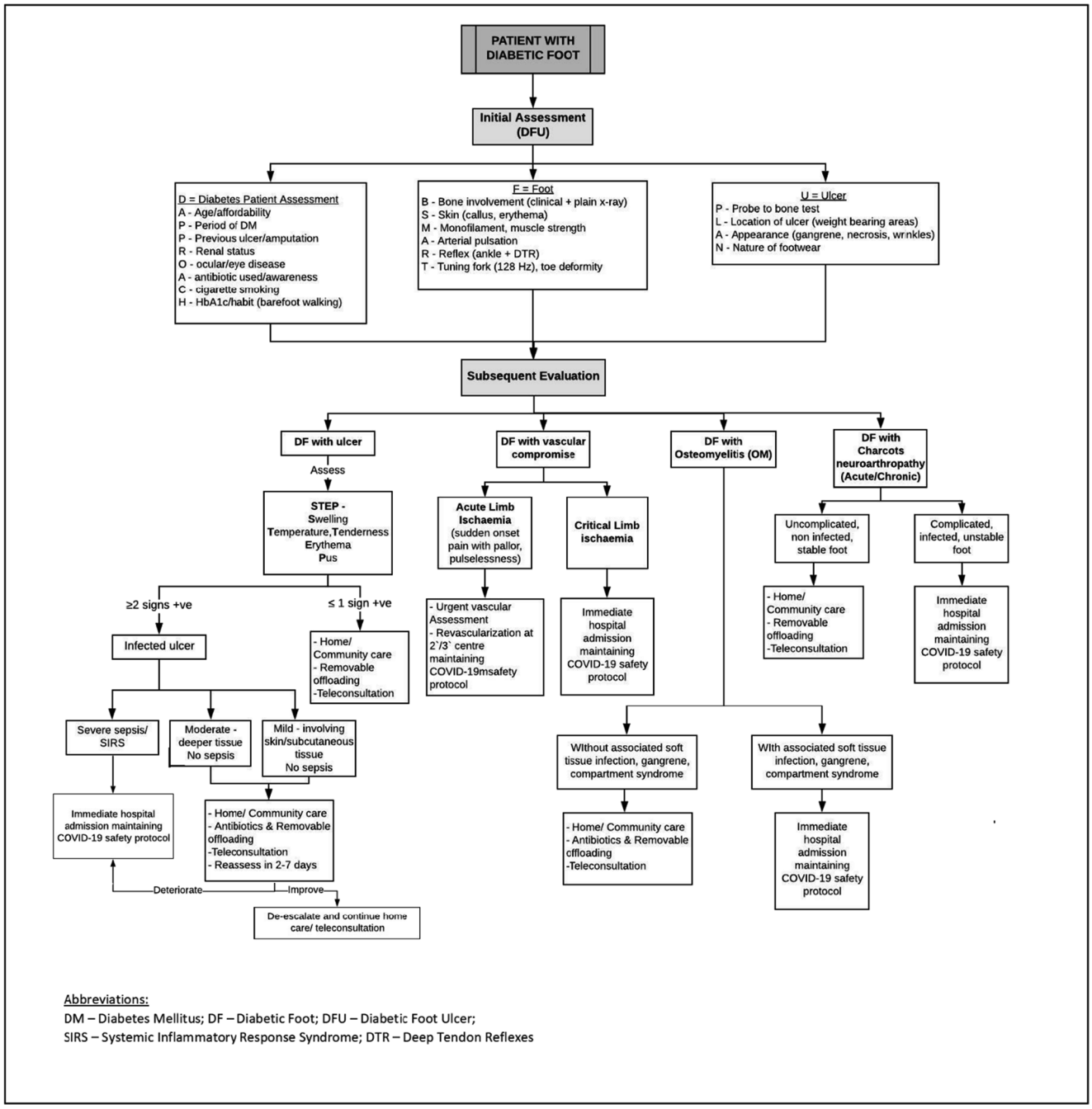

Fig. 2 Approach to management of diabetic foot care in the COVID-19 pandemic in India

In patients with complicated DFU who require a clinic or hospital visit, novel strategies including shifting the foot care facility to a medical office building outside the physical space of the COVID hospital, reducing crowding in the waiting area and expediting the evaluation and treatment of wounds can be implemented. Providing home-based intravenous antibiotics and early switchover to oral antibiotics are simple measures that can reduce the burden on the healthcare system which is already being stretched to capacity by the pandemic.

Conclusion

The COVID-19 pandemic has brought about healthcare disruptions of unprecedented magnitude, with diabetes patients bearing the brunt of the infection globally. Diabetic foot presents a clinical conundrum, where ingenious solutions are needed to provide optimal wound care while minimizing the exposure risk. Patients with DFU often have multiple comorbidities and fit several of the high-risk criteria for COVID-19 infection. Rather than avoiding these patients, it is imperative

to devise government-approved, telehealth-driven structured algorithms to treat them effectively. Since most existing international guidelines [43, 50] are suited to the western population, a modified triage and treatment algorithm has been suggested by the authors which may be (Fig. 2) more apt in tackling the dual menace of diabetic foot and COVID-19 in the Indian population.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Diagnosis and principles of management of gestational diabetes mellitus in the prevailing COVID-19 pandemic

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Abstract

Background Limited medical facilities are available due to Covid-19 pandemic. Nevertheless, all efforts should be made in planning judicial and possible methods of delivering health care, particularly to pregnant woman with GDM. GDM may play a crucial role in the increasing prevalence of diabetes and obesity and also may be the origin of cardiometabolic diseases.

Methods It is mandatary to diagnose and care pregnant woman with GDM. The test suggested to diagnose GDM has to be evidence based and in this regard "a single test procedure" evaluated meets this requirement. This doable test has been accepted by the Diabetes in Pregnancy Study Group India (DIPSI) and approved by MHFW-GOI, WHO, International Diabetes Federation, and International Federation of Obstetricians and Gynecologists. MHFW-GOI also recommends testing at first antenatal visit and then at 24–28 weeks of gestation. This opportunity can also be utilized for performing ultrasonography for assessing fetal development.

Result The first-line management is MNT and life style modifications. Non-responders may require insulin or OHA. The target glycemic control is FPG ~ 5.0 mmol/dl (90 mg/dl) and 2 h PPPG ~ 6.7 mmol/dl (120 mg/dl). The goal is to obtain newborns birth weight appropriate for gestational age between 2.5 and 3.5 kg, a step to prevent offspring developing diabetes.

Conclusion The essential precaution required during COVID pandemic is to wear face mask, avoid crowded places, and maintain social distancing. Finally, the economical and evidence based "single test procedure" of DIPSI is most appropriate for screening during the COVID pandemic.

Keywords Gestational diabetes mellitus (GDM) · Medical nutrition therapy (MNT) · Oral hypoglycemic agent (OHA) · Postprandial plasma glucose(PPPG) · Fasting plasma glucose (FPG) · Ministry of Health and Family Welfare · Government of India (MHFW-GOI)

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Introduction

The world has turned topsy-turvy with the COVID-19 pandemic. This will adversely affect the medical profession, particularly in the diagnosis and care of people with diabetes. This is going to result in an epidemic of diabetes. The prevalence of diabetes increasing globally forms 463 million in 2019 to 700 million in 2045, a 51% increase [1]. While several reasons are ascribed for this rising trend including aging population, urbanization, genetic predisposition, nutrition, and lifestyle transition, one factor that has not received adequate attention is glucose intolerance that occurs during pregnancy. GDM may play a crucial role in the increasing prevalence of diabetes and obesity [2]. In 2019, the global prevalence of hyperglycemia in pregnancy (HIP) in the age group 20–49 years was estimated to be 20.4 million or 15.8% of live births [1]. They had some form of hyperglycemia in

pregnancy, of which 83.6% were due to GDM [1].Thus, it has become necessary that all women should be screened for GDM even if they have no symptoms [3].

The prevailing opinion is that pregnant women do not appear more likely to contract the infection than the general population [4, 5].It is known that while pregnant women are not necessarily more susceptible to viral illness, pregnancy-related physiological changes influence their immune system and this can be associated with more severe symptoms [6], particularly true in the third trimester.

In the COVID pandemic times, widespread anecdotal evidence suggests that both clinicians and pregnant women are increasingly unwilling to recommend or undergo an OGTT [7]. The problem is the test results are available around 3 h after OGTT and then GDM women have to undergo additional health service visits for diabetes education, glucose monitoring review, and fetal ultrasonography, all of which carry exposure risk during a pandemic. Hence, there is a need for guideline which is universally acceptable [7].

Problems and solutions for screening

There are eleven guidelines to diagnose GDM [1]. The frequently recommended guideline is that of the International Association of Diabetes in Pregnancy Study Group (IADPSG) [8]. Presently, this guideline's importance is declining because of the comment that even at centers that accepted IADPSG recommendation, the approach varies and needs revision for standardization of the strategy for diagnosing GDM [9]. All the diagnostic criteria require women to be in fasting, but most of the time, pregnant women do not come in the fasting state because of commutation [10]. OGTT which requires three blood samples is resource intensive and many health services are not able to routinely perform an OGTT in pregnant women. Therefore, options which do not involve an OGTT are required. Furthermore, attending the first prenatal visit in the fasting state is impractical in many settings [10]. Even in developed countries (e.g., UK), a fasting blood test at the antenatal booking is often inconvenient [11]. The dropout rate is very high when a pregnant woman is asked to come again for the glucose tolerance test [10].

The guidelines and diagnostic criteria which are simple and feasible on the ground are important [12].A prospective study elucidated a test procedure that would not require a woman to be in the fasting state to diagnose GDM. The outcome of this study was, the 2-h plasma glucose ≥ 7.8 mmol/dl (≥ 140 mg/dl) with 75-g oral glucose administered to a pregnant woman in the fasting or non-fasting state, without regard to the time of the last meal was able to identify a woman with GDM [13–15]. The Diabetes in Pregnancy Study Group India (DIPSI) has accepted this "single test procedure" for diagnosing GDM. The National Institute of Clinical Excellence (NICE) guidelines also recommend 2-h PG ≥ 7.8 mmol/dl as one of the diagnostic criteria for GDM based on the study performed in the multi-ethnic population of UK [16]. This doable procedure is approved by the Ministry of Health & Family Welfare Government of India [17], WHO [10], FIGO [18], and IDF [19]. This procedure is being followed in Sri Lanka [20], Pakistan [21], Bangladesh [22], and may be in many other countries.

Diagnosis of GDM with 2-h PG ≥ 7.8 mmol/dl and treatment is worthwhile with a decreased macrosomia rate, fewer emergency cesarean sections, and serious perinatal morbidity, and may also improve the women's health-related quality of life [23, 24]. Furthermore, the advantages of this "single test procedure" are

a. Pregnant women need not be fasting.
b. It causes the least disturbance in a pregnant woman's routine activities.
c. It serves as both screening and diagnostic procedures (universal testing is possible).
d. Laboratory glucose measurement is often not available and testing with a portable plasma glucose standardized meter is the only option [10].
e. RCT shows the benefit of treating GDM women identified primarily by postload values [10].
f. There is no high-quality evidence that women and their fetuses benefit from treatment if only the fasting value is abnormal [10].
g. Fasting glucose measurement is insufficient for reliably ruling out GDM [25], particularly in non-Caucasian population [26].

In view of the above, DIPSI single test procedure may be most appropriate for screening during the COVID pandemic also.

Metabolic management during pregnancy

The guidelines are required to maintain maternal plasma glucose in the normal range by MNT and to recommend OHA or insulin whenever necessary for improved perinatal outcomes. The goal is to maintain fasting plasma glucose (FPG) ~ 90 mg/dl (5.0 mmol/dl) and 2-h postprandial plasma glucose ~ 120 mg/dl (6.7 mmol/dl) in GDM patients so as to avoid perinatal complications [27]. Managing GDM is like primary prevention of the disease for the next generation, as it helps to decrease the incidence of type 2 DM in the generations to come.

Management guiding principles

- All pregnant women who test positive for GDM for the first time should be started on MNT and physical exercise

for 2 weeks. Dietary intake is foundational to optimal pregnancy outcomes because nutritional quality and quantity have an important impact on the overall growth and development of the fetus.
- Women should walk/exercise (which she is used to) for 30 min or perform household work.
- Women with normal BMI (19.8–26.0 kg/m^2) have been recommended to gain a total of 11.4–15.9 kg; for the ones who are overweight (BMI 26.1–29.0 kg/m^2), the weight gain recommendation is 6.8–11.4 kg, whereas obese women with a BMI > 29 kg/m^2 are permitted weight gain only up until 7 kg.
- For women at high risk for excessive weight gain, interventions need to begin in the first trimester. Research on the pattern of maternal gestational weight gain shows that weight gained in the first trimester is more predictive of infant weight than the weight gained in the third trimester [28]. There was no increase in calories in the first trimester, an additional 340 kcal/day during the second trimester, and 452 kcal/ day during the third trimester [29].
- If 2-h postprandial plasma glucose (PPPG) remains > 6.7 mmol/dl with MNT and lifestyle changes, metformin or insulin therapy is recommended.

Medical nutrition therapy

Protein is the most important nutrient and one of the measures in the effort to prevent COVID-19. Protein is also important for immunity as the white blood cells are protein themselves and are the first line of defense mechanism to combat any infection and prevent it from affecting the body. In pregnancy 1.1 g of protein is needed per kilogram of ideal body weight. This would mean 60 to 70 g of protein. This has to come from grains, pulses, legumes, eggs, chicken, fish, and meat. Vitamin C is from Amla, zinc from whole grains, and milk products. Vitamin A is from orange and yellow vegetables, egg fish, and milk products. The sources of vitamin D are fish, egg, milk, and oils which are fortified. The sources of vitamin E are nuts, oils, and oilseeds. Selenium is present in milk, eggs, seafood, and chicken. Ginger, garlic, citrus, spinach, sunflower seeds, and red bell peppers are foods that support the immune system. Garlic can help the body to remove harmful toxins, stimulate immune responses, and reduce inflammation. A balanced meal with an emphasis on whole pulses, eggs, fish, chicken, vegetables, and fruits will provide the required nutrients to prevent COVID-19 in pregnant women and those with gestational diabetes also.

Drug management (metformin or insulin therapy)

- Metformin or insulin therapy is the accepted medical management of pregnant women with GDM not controlled on MNT. Insulin is the first drug of choice.
- Insulin can be started at any time during pregnancy for GDM if MNT fails.
- If a pregnant woman is not willing for insulin, metformin can be recommended provided gestational week is more than 12 weeks [30]. The starting dose of metformin is 500 mg twice daily orally up to a maximum of 2 g/day. If the woman's blood sugar is not controlled with the maximum dose of metformin (2 g/ day) and MNT, there is no other option but to advise insulin.
- Hypoglycemia and weight gain with metformin are less in comparison with Insulin.

Insulin therapy: (Fig. 1)

- The recommended starting dose of insulin in GDM is 0.1 unit/kg of body weight per day. The dose can be increased on follow-up until 2-h PPPG is around 6.7 mmol/dl.
- Rarely, a GDM woman may require more than 20 units of insulin per day. If she requires multiple doses of insulin, she may be referred to a higher center where the physician is available.

Monitoring glycemic control

- Fasting and 2-h PPPG can be monitored to adjust the drug dosage. But most importantly, monitoring 2-h PPPG is ideal as when 2-h PPPG is around 6.7 mmol/dl; FPG will never exceed 5.0 mmol/dl.
- Laboratory glucose measurement is often not available and testing with a portable plasma glucose standardized meter is the only option.
- The WHO (2013) guideline does not include HbA1c as a means of diagnosing diabetes in a pregnant woman and for monitoring [31]?
- Ideal will be monitoring as frequently as possible but must be every 2 weeks between the 24th and 28th week of gestation.
- After the 28th week every week until delivery.

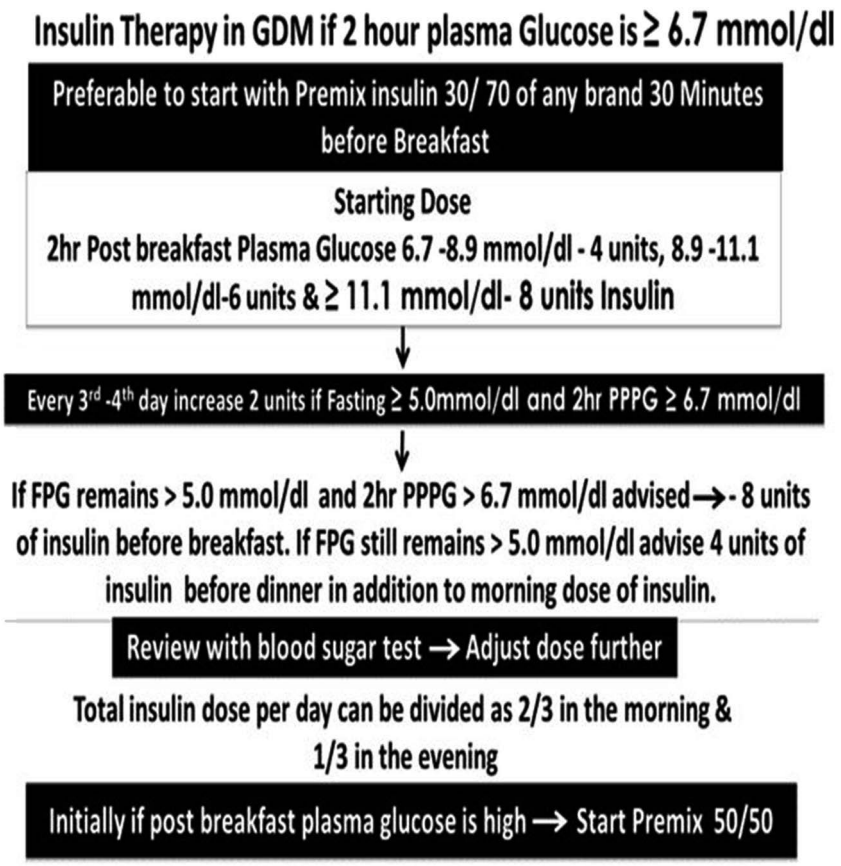

Fig. 1 Insulin therapy

Treatment modifications in the presence of the COVID-19 pandemic

As alluded earlier, pregnant women experience immunologic and physiologic changes. This might make them more susceptible to viral respiratory infections, including COVID-19. The need to safeguard the fetus adds to the challenge of managing their condition. Antenatal clinics with multiple and traditional face-to-face GDM education sessions now should go for remote delivery, using mobile health tools, interactive webinars, and online resources. If hospital attendance is not possible, blood sugar check-up with standardized glucometers is the alternative choice. After the first check-up and diagnosis of hyperglycemia, where glycemic targets are reached, there are no other risk factors for adverse pregnancy outcomes, and remote obstetric review at 36 weeks allows planning for delivery. But if glycemic and growth parameter targets are not met, or when other risk factors for adverse pregnancy outcomes are present, a face-to-face obstetric review is essential.

The International Federation of Gynecology and Obstetrics (FIGO) has come up with a global interim guidance on COVID-19. This highlights that there is no current evidence that pregnant women are more susceptible to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or that those infected are more likely to develop severe disease. Poon et al. observed that there is no evidence of vertical transmission [32] (from mother to fetus) but a recent publication documented vertical transmission is possible with no adverse outcome [33].

Special management during the pandemic of COVID 19
Recent publications make it evident about the association of COVID-19 infection in pregnancy with both severe maternal morbidities requiring intensive care and perinatal complications (preterm birth with consequent neonatal morbidity and even perinatal death). Also, the rate of cesarean deliveries among COVID-19 women is very high.

Each pregnant woman should be screened for COVID-19 infection before delivery. For an infected mother, with hyperglycemia, metformin should be continued as it exerts palliative against the infection until any acute complications like ketoacidosis or renal or respiratory failure develop. If not controlled, insulin should be started and will require a higher dosage for COVID-19-positive mothers as the infections damage the glycemic control by its effect on beta cells.

If steroid is used for COVID-19 infection or for fetal lung maturity, insulin dose needs to be increased. Many studies showed that outcomes are worse for patients with COVID-19 infection with corticosteroid use on the outcome of critically ill patients [34].

Antenatal magnesium sulphate given prior to preterm birth (32 gestational weeks) for fetal neuroprotection prevents cerebral palsy (CP) (risk higher with hyperglycemia in pregnancy) and reduces the combined risk of fetal/infant death or CP [35]. Though there is a possibility of a detrimental impact of magnesium sulphate on the respiratory depression in pregnant women with severe COVID-19 disease, appropriate administration with monitoring renal function and maintaining diuresis (≥ 30 mL/h) is not associated with serious maternal adverse effects [36]. Rather, magnesium has also a dilatory effect on bronchodilators, showing even beneficial effects on the pulmonary function in patients with severe asthma and decreasing the production of reactive oxygen species (ROS), which are elevated in patients with acute respiratory distress syndrome, a common complication of COVID-19 infection [37].

Postpartum care

All women who had GDM should be tested for glucose intolerance, 6 weeks after delivery. If FPG is ≥ 5.6 mmol/dl, she should be diagnosed to have impaired fasting glucose (IFG), and if 2-h postglucose is ≥ 7.8 mmol/d, she is diagnosed to have impaired glucose tolerance (IGT) with 75-g oral glucose.

If the GDM woman is on insulin, she may not require insulin immediately after the delivery and in the postpartum period. A GDM woman who was on metformin may be advised to continue if her postpartum blood glucose is ≥ 7.8 mmol/dl. Metformin can be consumed during breastfeeding. It is advisable to continue lactation for 2 to 6 months for delaying the development of diabetes in both the mother and her offspring.

Conclusion

During the COVID-19 pandemic, in order to decrease the risk of infection to pregnant women, it is important to restrict the number of visits to the healthcare facility. She has to take precautionary measures like the use of face masks and hand hygiene while maintaining physical distancing. In order to achieve these objectives, it will be even more pertinent to follow the "single test procedure" for diagnosing GDM. By adopting this procedure, the evaluation for GDM can be done in one visit. Even if the woman comes in the non-fasting state, by administering a 75-g oral glucose load, her plasma glucose can be estimated by taking a blood sample at 2 h. In some situations, the glucose load can also be taken at home and the pregnant woman can visit the hospital 2 h after the glucose ingestion to give a single sample for plasma glucose estimation. If a lab visit is not possible, a plasma glucose standardized glucometer can be used [10]. By this procedure, a prompt diagnosis of GDM can be made, while minimizing the risk of infection to the antenatal women visiting the healthcare facility.

The COVID-19 pandemic is a situation wherein everyone has to provide simple solutions to every problem and the "single test procedure" is ideally suited for screening all pregnant women with minimum contact. Medical nutrition therapy is the sheet anchor in the management of GDM. A woman who does not respond to meal plan and lifestyle modification may be advised insulin or metformin.

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SHORT ARTICLE

Management of children and adolescents having type 1 diabetes during COVID-19 pandemic in India: challenges and solutions

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Abstract

Purpose Type 1 diabetes (T1D) requires a holistic approach and continuous care. The current COVID-19 pandemic has made the health care professionals realise its challenges even more ardently than in the normal times. In a country like India with its huge population burden and a significant number of people having T1D, the risk of COVID-19 in people having T1DM is considerably high.

Methods In this article, we are sharing our practical experiences of problems faced by children and adolescents having T1DM during the past 2 months of lockdown.

Results We have classified the challenges into 3 broad categories based on diabetes self-management, healthcare system and psychosocial aspects. We have tried to provide precise, comprehensive and region specific solutions to these challenges. Solutions briefly include maintaining the supply chain of essentials like insulin, syringes and glucose meter strips to psychological support, financial aid and support for hospitalization in case of COVID-19 itself or diabetes complications including diabetic ketoacidosis.

Conclusions Children and adolescents having T1DM require special care and attention during this period of COVID-19 pandemic because of various challenges as discussed. Our proposed solutions may help them overcome these problems and help them in better diabetes management during such emergency situations.

Keywords Type 1 diabetes · COVID-19 · Challenges · Solutions

Introduction

As per IDF, there are estimated 1.1 million children and adolescents having type 1 diabetes (T1DM) globally [1]. India was home to 95,600 T1DM between 0 and 14 years of age in 2019 and about 15,900 new cases diagnosed every year in the same age group [1].

Currently, mankind is facing a global pandemic of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2], with 18,575,326 people infected in more than 200 countries and 7,01,754 people who have died, as per the WHO as of 6 August 2020 [3]. The Indian numbers have now risen to 19,64,536 total reported positive cases and 40,699 deaths [4].

Type 1 diabetes and COVID-19

A recent study (currently under peer review) from England demonstrated an independent association between the level of glycemia and COVID-19 mortality in people having T1DM or type 2 diabetes [5]. Another NHS-funded population cohort study reported 3.5 times more risk of in-hospital deaths with COVID-19 in people having T1DM as compared with those without diabetes [6]. The gaps in pediatric diabetes

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management can be bridged with the use of telemedicine, virtual diabetes clinics, and diabetes technology in the current COVID-19 situation [7].

As there is no definitive treatment or preventive vaccine for this viral infection, personal hand hygiene, respiratory etiquette, and social distancing are the most widely used strategies for the control of this highly contagious virus. Outbreak control measures to reduce the amount of mixing in the population include work from home, closure of academic organizations, and strict lockdown [8]. For this reason, a nationwide lockdown has been imposed in India from 25 March 2020 up to 30 June 2020 [9]. Lockdown, although effective in curbing the community transmission of this virus, has potential impact on people living with diabetes, particularly T1DM. We intend to enumerate the challenges being faced by the children and adolescents having T1DM and some solutions that have been proposed and worked out.

These challenges can be broadly divided into 3 categories as shown in Table 1.

1. Challenges related to diabetes self-management (DSM)

Skills of DSM are essential for children and adolescents having T1DM to improve or maintain glycemic control, to improve quality of life, and to minimize the risk of complications [10, 11]. For people living with T1DM, DSM includes regular insulin injections with proper technique, regular blood glucose monitoring, healthy eating, physical activity, problem-solving, and healthy coping [10]. Current situation of lockdown has had an impact on many components of DSM as described below.

Table 1 Classification of challenges faced by children and adolescents having T1DM during lockdown

(1) Challenges related to diabetes self-management (DSM)
(i) Insulin therapy
(ii) Glucose monitoring
(iii) Medical nutrition therapy
(iv) Physical activity
(v) Sick day management
(vi) Emergency preparedness
(2) Challenges related to healthcare system
(i) Routine healthcare support/medical specialist support
(ii) Emergency issues related to glucose control—hypoglycemia, DKA
(iii) Emergency issues related to COVID-19
(iv) Technical issues
(3) Challenges related to psychosocial aspects
(i) Psychological issues
(ii) Financial issues

(i) Insulin therapy: It is essential for survival in all people with T1DM. Children and adolescents with T1DM require multiple daily insulin injections (1–2 basal insulin injections plus at least 3 regular or rapid acting insulin injections) as per recommendation by the major organizations [12–14]. Many of these children and adolescents are supported by various programs (like Changing Diabetes in Children (CDiC) and Life for a child program) for regular supply of insulin and glucose meter strips [14]. This is being facilitated by local healthcare teams. Because of lockdown, many children residing in remote villages may not get regular insulin supplies because of closure of nodal healthcare facilities and local transport facilities.

Proposed solutions: Children and adolescents having T1DM should be able to reach nodal persons of supporting programs in case of inability to get insulin vials or cartridges. The Research Society of Study of Diabetes in India (RSSDI) has circulated the contact numbers of nodal persons of insulin manufacturers and supporting programs to people having T1DM and their doctors through email and social media. A dedicated helpline number, supported by diabetes educators and medical specialists, should be available to provide solutions to day-to-day problems. Unavailability of any type of insulin may require switching to another type so as to avoid risk of hyperglycemia and consequent DKA. One of the approved protocols suggests 20% reduction in insulin dose during switch from rapid acting insulin analogue to regular human insulin or vice versa to avoid hypoglycemia [15].

(ii) Glucose monitoring: Regular self-monitoring of blood glucose and continuous glucose monitoring at times is an essential component of T1DM management [16]. Lockdown may interrupt regular supplies of glucose meter strips to children and adolescents, being supported by programs like CDiC, because of closure of local nodal centers and local transport facilities.

Proposed solutions: RSSDI has circulated a list of contact numbers of nodal persons of glucose meter manufacturers and urine ketone strips to people having T1DM and doctors through email and social media.

(iii) Medical nutrition therapy: Because of strict lockdown and suspension of even vegetable supplies in certain areas, children and adolescents may not get regular supply of vegetables and fruits, an important component of their healthy eating plan [17]. There may be reduction in eating outside and consumption of junk foods because of lockdown, and this will probably have an impact on insulin requirements. However, no definite data related to this issue is available.

Proposed solutions: Local support groups like Juvenile Diabetes Foundation (JDF), in collaboration with local health authorities, should arrange for regular supply of milk, vegetables, fruits, and other essentials to these children and adolescents. Information booklets and animated videos related to healthy eating and healthy recipes may also be circulated through digital media.

(iv) Physical activity: Because of lockdown and stay at home orders, children and adolescents may not be able to participate in daily sports and playground activities [13] that may worsen their glycemic control.

Proposed solutions: Children and adolescents with T1DM should be encouraged to do indoor exercises by educating them through online tools as well as through social media. Because of closure of schools and colleges, they may get more time and should be encouraged for indoor physical activities. Use of animated videos featuring cartoon characters may prove useful in motivating children for indoor plays and exercises. Local support groups may also provide peer support for the same.

(v) Sick day management: During periods of stress and acute infections, reduced oral intake and increased release of stress hormones may impact blood glucose levels, thereby increasing the risk of both hyperglycemia and hypoglycemia [13]. Therefore, sick day management is particularly useful to avoid glycemic fluctuations and subsequent risk of DKA or hypoglycemia [18]. Lack of continuous insulin supply with lack of glucose monitoring may also increase the risk of hypo- or hyperglycemia.

Proposed solutions: Every child and adolescent with T1DM should be educated about sick day management rules at frequent intervals during lockdown with the help of information booklets and videos through social and digital media. These should be prepared in English, Hindi, and also local languages. Dedicated customer care helpline may assist them in better T1DM management during sick days, thereby reducing the risk of DKA and subsequent hospitalization.

(vi) Emergency preparedness: Emergency preparedness of T1DM children and adolescents and their families are very much lacking in our country. Any emergency situation like the current COVID-19 epidemic, resulting in panic, may worsen their glycemic control with consequent DKA.

Proposed solutions: Emergency preparedness plans can help children and adolescents having T1DM and their families in managing diabetes better during such emergencies. Sample emergency preparedness plan for use during lockdown has been proposed by authors as shown below in Table. 2.

2. Challenges related to the healthcare system

People having T1DM require continuous access to healthcare services. Lockdown may impact the access to healthcare services for their day-to-day management as well for their emergency issues like hypoglycemia, DKA, or any infection including COVID-19.

(i) Routine healthcare support for T1DM management: Because of lockdown and closure of healthcare services, children and adolescents may find it difficult to get medical support for their day-to-day management of T1DM as well as for management of their complications like diabetic neuropathy, retinopathy, and nephropathy.

Table 2 Emergency preparedness plan for T1DM management during Covid-19

A Portable, Insulated and waterproof diabetes emergency kit can be prepared, containing the following items

1. Keep all documents as mentioned in the green column in your kit. Soft copies or photos of all documents are to be stored in your mobile and shared with your parents or spouse or near friends.
2. Keep all ongoing medication (see yellow column) including insulin and glucose meter strips with adequate supplies for at least 4-6 week. Always check expiration date on all medications including insulin injections
3. Gel packs should be kept inside the freezer and should be added to cooler pack along with Insulin and unused injectable medications when ready to go. Do not use dry ice and avoid freezing the insulin.

Documents	**Medications/ supplies**	**Others (Materials)**
Identity Card- Adhar card	Insulin vials or cartridges	Batteries for glucose meters
Latest prescription paper of treating doctor	Insulin syringes or pen needles or pump supplies	A cooler pack with room for 4 gel packs
Latest Reports : HbA1c, S.Creatinine,Urine ACR, TSH,Hb,ECG	Other medications if any and O.T.C Medicines for pain, fever & vomiting	Empty plastic bottles or sharps containers for syringes, needles & lancets
Health Insurance Card	Glucagon kit	Hand sanitizer- at least 2
Documents of last 1 year of diabetes, documents of allergies, surgeries or any other medical illness	Glucose meter with strips (at least 100 strips for 30 days period) and pricking devices (lancets)	Tissue papers
Contact number of family physician or child specialist, diabetes specialist , pharmacist & parents	4 gram Glucose tablets (at least 20) or small juice boxes or hard candies or small plastic bottle of honey	Alcohol swabs
Customer care number of manufacturer of Glucose meter /insulin/ insulin pump	One additional glucose meter of same company	Paper soap or soap

HbA1c- Glycated Hemoglobin A1c, Hb- Hemoglobin, *S*.-Serum, *ACR*- Albumin creatinine ratio, *TSH*- Thyroid stimulating hormone, *ECG* - Electrocardiogram, *O.T.C*- Over the counter

HbA1c Glycated hemoglobin A1c, *Hb* hemoglobin, *S* serum, *ACR* albumin creatinine ratio, *TSH* thyroid-stimulating hormone, *ECG* electrocardiogram, *O.T.C* over the counter

Proposed solutions: Telemedicine guidelines, by the Ministry of Health and Family Welfare, Government of India, may be followed to provide medical support to them for issues related to insulin dose adjustment and management of their complications [19]. This may be further improved by creating virtual diabetes clinics providing support of nutritionist, physiotherapist, diabetes educator, podiatrist, as well as specialist services. Similarly, web-based tools may be used to educate them about diabetes self-management including foot care [11].

(ii) Emergency issues related to glucose control: Emergency issues like hypoglycemia or DKA requiring hospitalization may be precipitated by lack of proper DSM, stress, and acute infections in these subjects. During lockdown, there may be difficulties in getting hospitalized mainly in remote areas because of lack of transport facilities and lack of availability of beds in COVID-19 affected areas.

Proposed solutions: Children and adolescents along with their families should be educated frequently through online videos about symptoms and management of hypoglycemia as well as DKA. They should be provided with glucose tablets for emergency management of hypoglycemia and should be repeatedly educated about rule of 15 for hypoglycemia management. In case of emergency conditions requiring hospitalization, local support groups like JDF as well as concerned healthcare providers may assist them in getting hospitalized at the nearest healthcare center by providing ambulance services and local support.

(iii) Emergency issues related to COVID-19 or other infections: Children and adolescents having T1DM may develop COVID-19 or any other infection requiring hospitalization. Infections may also result in glycemic fluctuations and may increase the risk of DKA or hypoglycemia further increasing the chances of hospitalization [18].

Proposed solutions: In case of COVID-19, local health authorities should be immediately informed for testing and admission at dedicated COVID-19 centers with the help of local support groups like JDF. People having T1DM and their families should keep handy all their healthcare records including blood sugar log book for review by hospital team. Local healthcare team should coordinate with the hospital team for better T1DM management.

(iv) Technical issues: People having T1DM require use of technology in the form of glucose meters, pricking devices, insulin pens, as well as insulin pumps for routine management. During lockdown, they may not get support to resolve their technical issues because of unavailability of transport services and skilled personnel. Technology-related problems like pump dysfunction may result in unwanted hyperglycemia with consequent DKA.

Proposed solutions: People having T1DM should be provided with 24/7 technical support either onsite or through telecommunication, for successful use of these devices for insulin therapy as well as for glycemic monitoring.

3. Challenges related to psychosocial aspects

Children and adolescents having T1DM are already at risk of psychosocial issues because of the impact of disease on them and their families. This may be further aggravated or precipitated by lockdown.

(i) Psychological problems: Children and adolescents with T1DM because of social stigma and other issues related to T1DM are already prone to psychological problems like anxiety, phobia, etc. [12, 20]. Fear of COVID-19, closure of schools and colleges, and restrictions imposed by strict lockdown may impact their mental health and further increase the risk of psychological problems in them.

Proposed solutions: Local help groups run by JDF along with educational institutions can provide mental support by engaging children and adolescents in online educational and fun-filled activities. Yoga and meditation may be taught through online platforms to provide them psychological support. Educational institutions may start routine class work through online platforms to keep them busy and engaged in their studies. Information booklets to clear myths and doubts about COVID-19 may help in reducing fear and anxiety related to this disease.

(ii) Financial problems: Financial problems are the most negative aspect of this extreme lockdown. Children and adolescents of lower as well middle socioeconomic status may be hit very hard by financial problems of their parents. This may be due to salary cut, unemployment, and loss of daily wages making it difficult to follow proper T1DM management for them.

Proposed solutions: These vulnerable families definitely require assistance in the form of free insulin and glucometer strip supplies through programs like CDiC. Organizations like RSSDI and support groups like JDF may employ such parents as educators to provide DSM education to others having T1DM. Donors should be sought for to provide financial assistance to such vulnerable families through social media.

We can briefly summarize that children and adolescents having T1DM require special care and attention during this period of COVID-19 pandemic because of various issues as discussed above. Proposed solutions in this article may help them overcome these problems and help them in better diabetes management during such emergency situations with reduction in the risk of complications particularly DKA. We need to conduct proper prospective studies to identify the problems faced by children and adolescents with T1DM during lockdown and their impact on glycemic control and complications. This may help us to develop precise solutions to improve T1DM management during such pandemic.

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ORIGINAL ARTICLE

Impact of glycemic control in diabetes mellitus on management of COVID-19 infection

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Abstract

Background Diabetes mellitus may be associated with increased severity and enhanced mortality in COVID-19 infections. The present study was undertaken to evaluate the clinical presentation, laboratory parameters, radiological imaging, management, and outcome of COVID-19 infection in patients of diabetes mellitus and its association with glycemic control.

Methods The present study was designed to evaluate the difference between uncontrolled and controlled diabetes for COVID-19 manifestations by enrolling 80 admitted COVID-19 patients. Patients were categorized into two groups, where group 1 had patients with uncontrolled diabetes as indicated by HbA1c > 8 g% and group 2 had patients with controlled diabetes as indicated by HbA1c < 8 g%. Information concerning medical history, clinical manifestations, laboratory findings, radiological imaging, management, and outcome was extracted from medical records for evaluation, interpretation, and association among both the groups.

Results COVID-19 patients with uncontrolled diabetes exhibited a severe symptomatic presentation, excessive uncontrolled inflammatory responses, and hypercoagulable state. Total leukocyte count, neutrophil-lymphocyte ratio, serum levels of IL-6, FDP, and D-dimer were significantly raised ($p < 0.05$) in case of uncontrolled diabetes as compared with controlled diabetes. Radiological findings detected by chest radiograph and computed tomography chest suggested severe lung involvement in uncontrolled diabetes. COVID-19 patients with uncontrolled diabetes required intensive treatment as compared with controlled diabetes group in terms of insulin therapy ($p = 0.0226$) and non-invasive ventilation ($p = 0.0292$). Patients with uncontrolled diabetes had higher mortality ($p = 0.0375$) and required prolonged hospitalization ($p = 0.0479$) as compared with controlled diabetes group.

Conclusion From the current study, it can be concluded that uncontrolled diabetic condition might be a risk factor for severity and morbidity of COVID-19 patients. Uncontrolled diabetes mellitus might be responsible for an overall higher susceptibility for COVID-19 infection and severity in terms of symptomatic presentation, inflammatory storm, rapid pulmonary invasion, requirement of more intensive treatment, and a poor outcome.

Keywords COVID-19 · Diabetes mellitus · HbA1c · Glycemic control · Management

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Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) was the pathogen behind coronavirus disease (COVID-19) that emerged from Wuhan in China and was rapidly spread across most of the nations worldwide. The disease presentation may range from an asymptomatic state to a severe pneumonia associated with acute lung failure [1]. COVID-19 incubation period may range from 2 to 14 days. The usual presentation in COVID-19-positive patients has been fever, cough, shortness of breath, fatigue, loss of appetite, sputum production, joint pain, nausea, vomiting, and diarrhea. A large number of patients may not exhibit noticeable symptoms. A severe disease could be associated with fatal complications such as pneumonia, acute respiratory distress

syndrome (ARDS), multi-organ failure, septic shock, disseminated intravascular coagulation, and ultimately leading to death [2, 3]. The total number of confirmed COVID-19 cases worldwide have risen to 6, 644, 011 with 391, 839 deaths as of 6 June 2020. India, a nation already been the diabetes capital of the world, has reported 236, 657 cases of COVID-19 with 6642 deaths [4].

Angiotensin-converting enzyme 2 (ACE2) has been identified as a surface receptor responsible for SARS coronavirus (SARS-Co-V) invasion in human cells with direct interaction with its spike glycoprotein (S protein) [5]. Moreover, a ten to twenty-fold higher affinity of ACE2 towards receptor-binding domain (RBD) of SARS-CoV-2 as compared with the RBD of SARS-Co-V has been suggested. This might be the plausible explanation of ACE2 serving as a receptor for SARS-CoV-2 invasion [6]. Diabetes mellitus has already been a leading cause of morbidity worldwide, that is capable of affecting almost each and every system of the body [7]. Consequently, a deregulated immune system might develop, predisposing to various infections in diabetic patients [8]. ACE2 has anti-inflammatory effects, and its expression is found reduced in patients of DM possibly due to glycosylation. This might explain the occurrence of a severe acute lung injury and ARDS in diabetic patients. This makes diabetic population with or without other comorbidities susceptible to a higher morbidity and mortality due to COVID-19. A severe disease in such patients requires intensive approach to manage COVID-19.

The prevalence of diabetes in India is high, and paucity of data on its association with COVID-19 warrants identification of factors responsible for severe outcome in such patients. The present study was designed in this context to evaluate the association between glycemic control in diabetes mellitus patients with progression and prognosis of COVID-19 in patients admitted to the S.M.S. Medical College and Attached Hospitals, Jaipur, a premier tertiary care center in India. The study was also aimed at evaluating the association of clinical presentation, severity of disease, management, and outcome in patients of diabetes mellitus with uncontrolled and controlled blood sugar levels.

Method

Study design

The present retrospective, observational study was conducted on eighty COVID-19 patients with known cases of type 2 diabetes mellitus (T2DM) already on antidiabetic medications, admitted to S.M.S. Medical College and Attached Hospitals, Jaipur, Rajasthan, India. Based upon the glycemic control, all patients of T2DM were categorized into two separate groups. Group 1 had T2DM patients with poorly controlled blood sugar levels as indicated by HbA1c more than 8 g%. Group 2 included patients of T2DM, with controlled blood sugar levels as indicated by HbA1c less than 8 g%. Both of these groups were matched for age, gender, and absence of other comorbidities. In order to negate the implication of other comorbid conditions, we have taken into consideration COVID-19-positive patients with known to type 2 diabetes mellitus only and no other health-related chronic issues.

Data collection

The diagnosis of COVID-19 was based on the World Health Organization interim guidance, wherein confirmed cases were positive on reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [1]. Patients of T2DM after exclusion of other comorbidities were segregated and categorized in two groups based on their glycemic control. Information regarding epidemiological data, medical history, clinical manifestations, laboratory findings, chest radiograph (CXR) findings, ultrasonography (USG) chest, high-resolution computed tomography (HRCT) scans of the chest, diabetic complications, treatment, and outcome was extracted from medical records of admitted patients. The laboratory findings were based upon hemogram, c-reactive protein (CRP), ferritin, fibrin degradation product (FDP), D-dimer, and interleukin-6 (IL-6). Radiological findings were inferred using average visual score from digital chest radiograph (CXR) (scored from 0 to 4 according to visual assessment of involved lung area) [9], average severity score from USG chest (classified on sliding scoring scale of severity on the basis of 14 zone severity scores ranging from 0 to 42) [10], CT severity score from HRCT chest (assigned out of 25 based upon percentage area involved in each of the 5 lobes) [11], and proportion of patients with CT severity scores > 10/25. The data of patients with diabetes complications, particularly diabetic ketoacidosis and septic shock, was collected. Data regarding treatment among both groups by the use of hydroxychloroquine (HCQ), lopinavir-ritonavir combination therapy (LPV/r), ICU care, and non-invasive ventilation (NIV) was also collected. Outcome of COVID-19-infected patients was measured by the number of recovered patients, duration of seroconversion (duration from first positive to first negative RT-PCR for COVID-19), duration of hospital stays, and number of deaths during the course of treatment. The collected data was compiled, tabulated, interpreted, and correlated in both the groups to establish differences in COVID-19 manifestations on the basis of glycemic control in T2DM.

Statistical analysis

The descriptive statistics for quantitative data was expressed as mean and standard deviation, and qualitative data was

expressed as proportions. The parameters were compared among different groups using chi-square and z-score test for significant differences. The level of significance was assigned at a p value less than 0.05.

Results

In the present study, 22 patients (27.50%) had poorly controlled blood sugar levels with HbA1c level more than 8 g% and belonged to group 1, whereas 58 patients (72.50%) had controlled blood sugar levels with HbA1c level less than 8 g% that belonged to group 2. The mean age of SARS-CoV-2-infected patients with T2DM was 61.45 years (95% CI: 61.45 ± 5.08, SD = 11.59). Mean age of uncontrolled diabetes group was 63.2 years (95% CI: 63.2 ± 4.35, SD = 4.96), whereas mean age in controlled diabetes group was 60.86 years (95% CI: 60.86 ± 6.67, SD = 13.18), and the difference was non-significant ($p = 0.489$) (Table 1). There were no significant gender differences among the groups ($p = 0.301$). Other comorbidities with COVID-19 have not been considered to understand entirely the impact of uncontrolled glycemic condition on predisposition and severity in COVID-19-infected patients.

Clinical presentation Overall, 24 patients (30.00%) had symptomatic presentation. Group 1 (50.00%) exhibited a significantly greater ($p = 0.0164$) symptomatic presentation as compared with group 2 (22.41%). Most of the COVID-19-infected patients with T2DM presented with cough (16.25%), fever (15.00%), shortness of breath (11.25%), and sore throat (8.75%). A few patients also reported for headache (5.00%), chest pain (3.75%), and symptoms (5.00%) like pain in the abdomen, vomiting, diarrhea, and altered sensorium. Cough (31.82% in group 1 vs 10.34% in group 2) and shortness of breath (22.73% in group 1 vs 6.90% in group 2) were found more often ($p < 0.05$) in uncontrolled diabetes group compared with controlled diabetes group with p values 0.0203 and 0.0455, respectively.

Laboratory findings (Table 1) The blood profile of both the groups showed normal total leukocyte counts (TLC) with an average TLC 7.48×10^9/L ± 4.23, platelet count 2.12 Lac/μl ± 0.64, and neutrophil/lymphocyte (N/L) ratio 3.15 ± 1.98. However, uncontrolled diabetes group showed higher TLC and N/L ratio, i.e., 9.01×10^9 and 3.98, as compared with controlled group with values 7.01×10^9 ($p = 0.0403$) and 3.00 ($p = 0.0495$). The other laboratory parameters taken into consideration were as follows: c-reactive protein, ferritin, fibrin degradation product, D-dimer, and interleukin-6. The biochemical parameters were found to be more significantly variable among the two groups of patients. The parameters such as FDP 43.22 μg/L vs 24.69 μg/L ($p = 0.0433$), D-dimer 6.78 μg/L vs 4.05 μg/L ($p = 0.047$), and IL-6 levels 78.52 pg/mL vs 50.32 pg/mL ($p = 0.0256$) were observed to be elevated in group I patients in comparison with group II patients.

Radiological findings For the assessment of lung involvement in sample population, digital chest radiograph (CXR) of all patients, USG chest of 16 patients (20.00%), and HRCT chest of 30 patients (37.50%) were available. CXR represented classic for COVID-19 images in 20 patients (25.00%) with an average visual score of 0.78 ± 0.90 out of 4. USG severity score was 16.14 ± 11.32 out of 42. The average CT severity score was 7.4 ± 6.75 out of 25 with CT severity score > 10/25 in 12 patients (40.00%). CXR average visual score was significantly ($p = 0.0439$) higher in group 1 (1.12) than group 2 (0.68). CT severity score was significantly ($p = 0.0489$) higher in uncontrolled diabetes group (11.96) as compared with controlled diabetes group (6.1) with a CT severity score > 10/25 in 75.00% and 27.27% patients in respective groups ($p = 0.0182$).

Diabetic complications Six patients (7.50%) developed diabetic ketoacidosis (DKA), and nine patients (11.25%) had septic shock. DKA developed more often ($p = 0.0257$) in patients of uncontrolled diabetes (18.18%) as compared with the controlled diabetes group (3.45%). Septic shock was observed in 22.73% patients of uncontrolled diabetes, whereas it was 6.90% in controlled diabetes group.

Analysis of severity, management, and treatment in the two groups An observed comparison of uncontrolled and controlled glycemic patients showed that uncontrolled diabetic patients (68.18%) required insulin therapy more often ($p = 0.0226$) than the controlled group (39.66%). Requirement of non-invasive ventilation was significantly more in uncontrolled diabetes group as compared to controlled diabetes group patients ($p = 0.0292$), along with higher ICU care requisite for group I, whereas the need of LPV/r combination therapy for COVID-19 treatment in standard dosage did not differ significantly ($p = 0.1498$) between the two groups.

Outcome In total, 80 patients were considered; out of that, 40 patients (50.00%) recovered, whereas 14 patients (17.50%) succumbed to COVID-19, and remaining patients were undergoing treatment until the date this study was compiled. Average duration of hospital stays was significantly prolonged ($p = 0.0479$) in patients with uncontrolled diabetes (16.94 days) as compared with patients with controlled diabetes (13.91 days). As observed from the collected data, the average recovered patients of uncontrolled diabetic group were very low (36.36%) in comparison with group 2 (55.17%). Not only this, significantly, higher COVID-19-

Table 1 COVID-19 manifestation in patients with diabetes mellitus and their correlation with glycemic control

Characteristics	Total no./mean value ($N = 80$)	Group 1: Hb1Ac > 8 g/dL ($N = 22$)	Group 2: Hb1Ac < 8 g/dL ($N = 58$)	p value
Age	61.45 year (95% CI: 61.45 ± 5.08, SD = 11.59)	63.2 year (95% CI: 63.2 ± 4.35, SD = 4.96)	60.86 year (95% CI: 60.86 ± 6.67, SD = 13.18)	0.489
Gender				
Male	46 (57.5%)	12 (54.54%)	34 (58.62%)	$_x2 = 1.069$, $p = 0.301$.
Female	34 (42.5%)	10 (45.45%)	24 (41.38%)	
Clinical features				
Symptomatic patients	24 (30.00%)	11 (50.00%)	13 (22.41%)	$z = 2.404$, $p = 0.0164$
Fever	12 (15.00%)	3 (13.64%)	9 (15.52%)	$z = 0.210$, $p = 0.833$
Cough	13 (16.25%)	7 (31.82%)	6 (10.34%)	$z = 2.324$, $p = .0203$
Shortness of breath	9 (11.25%)	5 (22.73%)	4 (6.90%)	$z = 2.000$, $p = 0.0455$
Sore throat	7 (8.75%)	2 (9.09%)	5 (8.62%)	$z = 0.0665$, $p = 0.9442$
Headache	4 (5.00%)	1 (4.55%)	3 (5.17%)	$z = 0.1149$, $p = 0.9124$
Chest pain	3 (3.75%)	1 (4.55%)	2 (3.45%)	$z = 0.2306$, $p = 0.8181$
Other	4 (5.00%)	2 (9.09%)	2 (3.45%)	$z = 1.034$, $p = 0.3030$
Laboratory investigation				
Total leukocyte count ($\times 10^9$ /L)	7.48 × 10^9/L ± 4.23	9.64 × 10^9/L ± 7.11	7.01 × 10^9/L ± 4.01	$p = 0.0403$
Platelet (Lac/μL)	2.12 Lac/μl ± 0.64	2.34 Lac/μl ± 0.9	2.08 Lac/μl ±0.48	$p = 0.0989$
Neutrophil/lymphocyte ratio	3.15 ± 1.98	3.98 ± 2.26	3.00 ± 1.84	$p = 0.0495$
C-reactive protein (mg/L)	6.32 mg/L ± 3.89	7.25 mg/L ± 5.26	6.11 mg/L ± 3.48	$p = 0.2629$
Ferritin (ng/mL)	373.58 ng/mL ± 491.93	464.56 ng/mL ± 489.56	361.23 ng/mL ± 396.54	$p = 0.333$
FDP (μg/L)	30.28 μg/L ± 35.12	43.22 μg/L ± 43.93	24.69 μg/L ± 32.64	$p = 0.0433$
D-dimer (μg/L)	4.56 μg/L ± 5.98	6.78 μg/L ± 6.1	4.05 μg/L ± 5.12	$p = 0.047$
IL-6 (pg/mL)	58.60 pg/mL ± 53.82	78.52 pg/mL ± 70.64	50.32 pg/mL ± 48.52	$p = 0.0256$
Radiological imaging				
Chest radiograph	80	22	58	
Average visual score	0.78 ± 0.90	1.12 ± 1.04	0.68 ± 0.78	$p = 0.0439$
Classic for COVID images	20 (25.00%)	6 (27.27%)	14 (24.14%)	$z = 0.2891$, $p = 0.7718$
USG chest	16 (20.00%)	5 (22.72%)	11 (18.96%)	$z = 0.3756$, $p = 0.7039$
Average severity score	16.14 ± 11.32	17.21 ± 13.25	15.84 ± 10.84	$p = 0.8274$
HRCT chest	30 (37.50%)	8 (36.36%)	22 (37.93%)	$z = 0.1293$, $p = 0.8965$
CT severity score	7.4 ± 6.75	11.96 ± 8.62	6.1 ± 6.21	$p = 0.0489$
CT severity score > 10/25	12 (40.00%)	6 (75.00%)	6 (27.27%)	$z = 2.359$, $p = 0.0182$
Diabetic complication				
Diabetic ketoacidosis	6 (7.50%)	4 (18.18%)	2 (3.45%)	$z = 2.234$, $p = 0.0257$
Septic shock	9 (11.25%)	5 (22.73%)	4 (6.90%)	$z = 2.000$, $p = 0.0455$
Treatment				
Insulin therapy	38 (47.50%)	15 (68.18%)	23 (39.66%)	$z = 2.281$, $p = 0.0226$
Lopinavir-ritonavir	11 (13.75%)	5 (22.73%)	6 (10.34%)	$z = 1.436$, $p = 0.1498$
ICU care	5 (6.25%)	3 (13.64%)	2 (3.45%)	$z = 1.680$, $p = 0.0929$
Non-invasive ventilation	4 (5.00%)	3 (13.64%)	1 (1.72%)	$z = 2.182$, $p = 0.0292$
Outcome				
Recovered patients	40 (50.00%)	8 (36.36%)	32 (55.17%)	$z = 1.502$, $p = 0.1336$
Death	14 (17.50%)	7 (31.82%)	7 (12.07%)	$z = 2.075$, $p = 0.0375$
Duration of seroconversion	7.38 days (95% CI: 7.38 ± 2.01, SD = 6.42)	8.12 days (95% CI: 8.12 ± 2.84, SD = 7.98)	7.08 days (95% CI: 7.08 ± 1.85, SD = 6.18)	$p = 0.5614$
Duration of hospital stay	14.61 days (95% CI: 14.61 ± 1.89, SD = 5.80)	16.94 days (95% CI: 16.94 ± 2.80, SD = 6.45)	13.91 days (95% CI: 13.91 ± 1.69, SD = 5.34)	$p = 0.0479$

related mortality was observed in uncontrolled diabetes group (31.82% vs 12.07%).

Discussion

In our study, we have observed that uncontrolled diabetes has significantly altered the biochemical parameters along with worsening of prognosis. Diabetes mellitus predisposes an individual to a certain type of infection and mortality [12] including the COVID-19, although its risk as associated comorbidity in COVID-19 needs further exploration. The prevalence of T2DM in India is 7.3% [13], thereby predisposing a large proportion of population to COVID-19 and its complications. Type 2 diabetes mellitus as a consequence of metabolic syndrome and obesity predisposes to immune dysfunction with raised inflammatory factors and chemokines [14, 15]. ACE2 possessing anti-inflammatory property has been linked to SARS-CoV-2 invasion in human cells, and its expression is found reduced in patients of diabetes mellitus, possibly due to glycosylation [16]. This might explain higher predisposition of COVID-19 patients with diabetes mellitus to severe acute lung injury and ARDS [16]. Immunostaining technique has revealed an enhanced staining characteristic for ACE2 in islet tissue as compared with the exocrine pancreatic tissues suggesting a plausible role of coronavirus in islet destruction [17]. Thus, COVID-19 might lead to a sharp fluctuation in blood glucose level in diabetes patients, adversely affecting the varied clinical presentation of the disease.

In the present study, clinical presentation was more pronounced in uncontrolled diabetes group as compared with controlled diabetes group. Cough and shortness of breath occurred more often in uncontrolled diabetes patients, and the underlying cause for such presentation might be early and extensive lung involvement in COVID-19 infection due to glycemic variation. This was evident by baseline CXR findings of the study that suggested a higher proportional lung involvement in uncontrolled diabetes group as compared with controlled diabetes group. Moreover, a high CT severity score also indicated extensive lung involvement in uncontrolled diabetic patients. The aforementioned clinical picture supported by radiological findings suggested a severe pneumonia in uncontrolled diabetic patients as compared with the controlled diabetic patients.

The average total leukocyte count was observed higher in uncontrolled diabetes that could be attributable to an increased secondary inflammatory response in these patients. Neutrophil to lymphocyte ratio was also raised in peripheral blood of uncontrolled diabetes patients, possibly due to neutrophilia or a relative lymphocytopenia as a consequence of COVID-19 infection. Furthermore, the serum levels of inflammatory biomarkers such as IL-6, ferritin, and CRP were alarmingly raised in uncontrolled diabetes group. IL-6 is a predictor of disease severity and prognosis [18], and in a study conducted by Huang et al., it was reported that levels of IL-6 were elevated along with significantly reduced lymphocyte count, in patients with SARS-CoV-2 infection [19]. Excessively raised ferritin level is an indicator of activation of the monocyte-macrophage system that contributes significantly to the inflammatory storm associated with COVID-19 [20]. In the present study, raised ferritin levels were observed in uncontrolled diabetes, suggesting a higher susceptibility of such patients for an inflammatory storm, responsible for rapid deterioration due to COVID-19. Inflammation-associated hypoxia might induce thrombin activation with a consequent unfolding of exogenous coagulation pathway [20]. Inflammatory storm in COVID-19 is associated with significant rise in D-dimer levels, and similar pattern has been observed in our study as well where uncontrolled glycemic patients had significantly increased levels of D-dimer as compared with controlled diabetic patients. This finding is an indication of a hypercoagulable state and even disseminated intravascular coagulation in such patients. Patients of uncontrolled diabetes mellitus were more prone to develop diabetic complication during the natural course of COVID-19 as compared with the controlled diabetes group. Patients with uncontrolled diabetes developed diabetic complication like diabetic ketoacidosis and septic shock, more often.

Patients with uncontrolled diabetes mellitus required aggressive pharmacological and supportive treatments compared with controlled diabetes group as is much evident from more frequent requirement of insulin therapy in group I. Moreover, need of supportive therapies such as non-invasive ventilation and ICU care was also higher in uncontrolled diabetes patients. A low recovery rate, high mortality, and prolonged hospitalization indicated poor outcome in patients with uncontrolled diabetes mellitus as compared with control glycemic group of diabetes mellitus.

Conclusion

In the current retrospective study, we have considered 80 COVID-19-infected patients with T2DM and characterized them with biochemical, radiological, and other required clinical parameters. From the various observations, it can be concluded that uncontrolled diabetes mellitus may predispose an individual to a severe and fatal COVID-19 infection. The severity of COVID-19 in diabetics could be attributable to the dysfunctional immune system, with a simultaneous susceptibility to viral infection and an exaggerated immune response like cytokine storm. Such a status of immunity provides a favorable condition for viral survival and longer recovery duration in diabetics. COVID-19 patients with uncontrolled diabetes require higher attention in terms of pharmacological and supportive treatment than those with controlled diabetes

group. A high prevalence of T2DM in India predisposes a large proportion of population to COVID-19 and its complications. HbA1c more than 8 g% in patients with uncontrolled diabetes mellitus should be considered a risk factor for an overall higher susceptibility for COVID-19 infection and severity in terms of symptomatic presentation, inflammatory storm, rapid pulmonary invasion, requirement of more intensive treatment, and a poor outcome. Hence, an extreme care for preventing COVID-19 in people with underlying DM is advisable beside an intensive care in already infected individuals.

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Authors' contributions S. Bhandari, G. Rankawat, and A. Singh formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; G. Rankawat and A. Singh collected and analyzed the data for study. G. Rankawat wrote the manuscript. S. Kakkar and V. Gupta conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Data availability Available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the ethical and research committee of the SMS Medical College Hospital, Jaipur, India. All ICMR guidelines have been duly followed.

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ORIGINAL ARTICLE

COVID-19 pandemic: a double trouble for Indian adolescents and young adults living with type 1 diabetes

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Abstract

Background Strict isolation measures and interrupted health care services during the COVID 19 pandemic are contemplated to instigate stress universally, particularly in those with chronic illnesses such as type 1 diabetes (T1D).

Methods A cross-sectional, observational study was done to assess determinants of stress and its impact on glycemic control in adolescents and young adults (aged 12–24 years) living with T1D in India. An online, semi-structured survey including Perceived Stress Scale (PSS-10) was distributed and results were analyzed.

Results A total of 89 participants (46 males, mean age 19.61 ± 3.8 years) with T1D completed the survey. Age ($r = 0.325$, $p = 0.005$) and HBA1C level within the preceding 3 months ($r = 0.274$, $p = 0.036$) correlated positively with PSS-10 scores. There was a statistically significant difference in PSS-10 score based on gender ($t(70) = -2.147$; $p = 0.035$), education ($F(4,67) = 4.34$, $p = 0.003$), and occupation ($F(3,68) = 4.50$, $p = .006$). On multiple linear regression, gender, occupation, and HbA1C were the significant determinants of PSS-10 ($F(3,55) = 12.01$, $p < 0.001$, $R^2 = 0.363$). One-way ANOVA showed a significant impact of mean PSS-10 score on the glycemic control ($F(2,69) = 3.813$, $p = 0.027$).

Conclusion An increased prevalence of stress was seen among Indian adolescents and young adults living with T1D. Female gender, salaried individuals, and pre-existing poorly controlled diabetes contributed to an increased risk of stress. Increased stress resulted in worsened glycemic control.

Keywords COVID-19 · PSS-10 · Type 1 diabetes · Adolescent

Introduction

Coronavirus disease (COVID-19), caused by a novel coronavirus SARS-CoV-2, is considered a close relative of severe acute respiratory syndrome (SARS) [1]. With the first COVID-19 case detected in December 2019 in Wuhan, Hubei province of China [2], it has spread rampantly, jeopardizing health infrastructure and economies across the globe. COVID-19 was officially declared a pandemic by the World Health Organization (WHO) on 11th March 2020 [3].

In the absence of an effective drug or vaccine against COVID-19, prevention is by far the best way to limit the infection [4]. In an attempt to mitigate the spread of the disease, an unprecedented practice of social distancing has been instituted across the nation [5]. Strict isolation measures, interruption in access to routine health care, compromised academic, and social activities are contemplated to instigate stress and anxiety among all, particularly those living with chronic illnesses, such as type 1 diabetes (T1D) [6].

T1D is one of the most common endocrine metabolic disorders around the world [7]. Individuals living with T1D are at an increased risk of psychological issues, owing either to the underlying disease, or due to the complexity involved in the management of diabetes [8]. Diabetes management mandates adherence to insulin, balanced diet, regular physical activity, and self-monitoring of blood glucose in order to achieve good glycemic control and prevent the development of short-term and long-term complications [9].

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Studies have reported the psychological impact of the COVID-19 pandemic on health care workers, children, and older adults [10–12]. However, there is scarcity of data regarding the psychological impact of COVID-19 on those living with chronic illnesses, such as T1D.

We believe that this is the first study to analyze the level of perceived stress among Indian adolescents and young adults living with T1D, using a validated psychometric tool (Perceived Stress Scale, PSS-10), and identify the determinants of stress and its impact on the glycemic control.

Methodology

This was a cross-sectional, observational study, involving known patients living with T1D. An online survey was designed using Google Forms and shared with the participants. The online link comprised of an informed consent followed by a semi-structured questionnaire. Participants were included if they were between 12 and 24 years, living with T1D, had an ability to understand simple English, had access to the internet, and were willing to participate in the study. Data collection was started on 30th April 2020 at 4 PM IST and closed on 10th May 2020 at 4 PM IST. After accepting to participate in the survey, participants were redirected to the four different sections of the questionnaire (Appendix I).

The first section included demographic details; the second included assessment of knowledge and attitude of participants towards COVID-19 (based on the information and recommendations provided by the World Health Organization [13] and the Ministry of Health and Family Welfare, India) [14]. Each question was awarded 1 point for the correct response and 0 for an incorrect response. The scores for transmission, prevention, and presentation were converted to percentages of total possible score. The third section evaluated the presence of stress among the participants using the ten-item Perceived Stress Scale (PSS-10) [15] and the techniques adopted to cope with stress. PSS-10 measures the psychological stress estimated over the previous 4 weeks. It consists of 10 items measured on a five-point Likert scale (0 never, 1 almost never, 2 sometimes, 3 fairly often, 4 very often). The total score is obtained by adding the scores of all the items, with reverse coding for items 4, 5, 7, and 8, as they are positively stated. The total score ranges from 0 to 40, with score 40 depicting the highest perceived stress level. Participants were categorized into "low stress" for PSS-10 score between 0 and 13, "moderate stress" for scores 14–26, and "high stress" if PSS-10 score between 27 and 40 [15].

The fourth section included questions pertaining to T1D, HBA1C within the preceding 3 months, change in frequency of self-monitoring of blood glucose (SMBG), self-assessed glycemic control based on SMBG, possible reasons for poor blood sugar control, and potential ways of allaying stress.

Statistical analysis

The data was compiled using Microsoft Excel and analyzed using IBM Statistical Package for Social Sciences (SPSS version 25.0, SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean (SD) and categorical variables as frequencies (percentages). Student's t test for independent samples and one-way ANOVA were used to compare the means of PSS-10 score among different groups of participants. Spearman correlation was used to test for correlation between non-parametric, continuous variables. Variables found to have a significant association with PSS-10 score on univariate analysis were entered as predictor variables into a multiple linear regression model, with PSS-10 score as the dependent variable. A p value of less than 0.05 was considered as significant.

Results

A total of 89 adolescents and young adults (46 males, mean age 19.61 ± 3.8 years), living with type 1 diabetes, with a mean duration of diabetes 8.4 ± 5.0 years and a mean HBA1C of 8.1 ± 1.5%, completed the survey. Majority were on basal bolus regime (80.9%) followed by split mix regime (13.5%); and a small proportion of them were on continuous subcutaneous insulin infusion (CSII; 5.6%). The baseline socio-demographic characteristics of the participants is depicted in Table 1.

All the 89 participants had either heard or read about the COVID-19 pandemic. The prime source of information was television (74.2%) followed by social media (67.4%), search engines (64%), print media (59.6%), and lastly government-authorized applications (53.9%). Around 78.7% ($n = 70$) of the participants were reportedly satisfied with the available information, with almost all (89.9%, $n = 80$) tracking pandemic-related information at least once daily. Table 2 details the performance of participants on questions regarding the transmission, prevention, and presentation of COVID-19 infection.

More than half of all the cases 51.7% ($n = 46$) reported moderate stress; low stress was perceived by 42.7% ($n = 38$) and severe stress was observed in 5.6% ($n = 5$). Age correlated positively with mean PSS-10 score ($r = 0.325$, $p = 0.005$). Females were found to have a significantly higher PSS-10 score compared with males (19.03 ± 5.39 versus 15.97 ± 6.61; $t(70) = -2.147$ $p = 0.035$). There was a statistically significant difference in PSS-10 score between respondents, based on their education ($F(4,67) = 4.34$, $p = .003$) and occupation (F $(3,68) = 4.50$, $p = 0.006$). A Tukey post hoc test showed that those in high school had significantly lesser PSS-10 score compared with the graduates ($p = 0.020$) and post-graduates ($p = 0.002$). Furthermore, Tukey post hoc test revealed that those employed had significantly higher PSS-10 score compared with students ($p = 0.020$).

Table 1 Baseline socio-demographic characteristics of the study participants

Variables	Type	Participants *n* (%)
Age (year)		19.61 ± 3.82*
Gender	Male	46 (51.7)
	Female	43 (48.3)
Marital Status	Married	2 (2.2)
	Unmarried	87 (97.8)
Residence	Independent house	67 (75.3)
	Apartment	20 (22.5)
	Hostel	2 (2.2)
Education	Less than high school	15 (16.8)
	High school	8 (9.0)
	Intermediate	13 (14.6)
	Graduation	41 (46.1)
	Post-graduation	12 (13.5)
Occupation	Student	63(70.8)
	Employed	13 (14.6)
	Business	7 (7.9)
	Unemployed	6 (6.7)

* Mean ± SD

Participants who were reportedly dissatisfied with the pandemic-related information were found to have significantly higher PSS-10 score ($F(2,69) = 3.440$, $p = 0.038$). A significant positive correlation was obtained between the mean PSS-10 score and HBA1C level within the preceding 3 months ($r = 0.274$, $p = 0.036$, Fig. 1). No significant association with PSS-10 score was observed for the type of residence, knowledge level regarding transmission, prevention, and presentation of COVID-19 infection, the frequency of seeking COVID-19-related information, presence of any suspected symptom over the last 14 days, duration of diabetes, and insulin regimen (Table 3).

On multiple linear regression analysis, age, gender, education, occupation, satisfaction with available information, and HbA1C were entered as predictor variables. On stepwise backward linear regression analysis, the model comprising gender, occupation, and HbA1C on PSS-10 score was significant with $F(3,55) = 12.01$, $p < 0.001$, $R^2 = 0.363$.

Reduced frequency of SMBG was reported by 55.1% ($n = 49$) of the participants. Based on self-assessment of SMBG over the last 1 month, improved glycemic control was reported by 42.7% ($n = 38$), worsened glycemic control by 13.5% ($n = 12$), and 43.8% ($n = 39$) reported no change. One-way ANOVA showed a significant impact of mean PSS-10 score on the glycemic control ($F(2,69) = 3.813$, $p = 0.027$). Self-reported worsening of glycemic control was significantly more common among those with a higher mean PSS-10 score compared with those who reported no change ($p = 0.021$). Table 4 enumerates the challenges faced by the participants in diabetes management and their potential solutions.

Among the various coping methods reported by the participants, spending time with friends and family was reported by the majority (78.6%), followed by pursuit of hobbies (61.1%) and praying (50%).

Table 2 Summary of correct responses for COVID-19-related information

COVID-19 transmission, prevention, and presentation	Participants *n* (%)
How does the COVID-19 infection spread?	
Direct contact with infected person	79 (88.8)
Droplet*	72 (80.9)
Airborne#	22 (24.7)
Do not know	3 (3.4)
How can you protect yourself from the COVID-19 infection?	
Frequent hand washing	84 (94.4)
Social distancing	84 (94.4)
Wearing a face-mask when outdoors	85 (95.5)
Avoiding contact with persons coughing/sneezing	81 (91.0)
Do not know	0
What are the presentation of COVID-19 infection?	
Fever	83 (93.3)
Dry cough	82 (92.1)
Tiredness	56 (62.9)
Cold	57 (64.0)
Diarrhea	24 (27.0)
Sometimes, no symptoms	57 (64)
Do not know	3 (3.4)

* Spreads when you come within 1 meter of someone coughing/sneezing.

The infection remains in the air for long periods of time, even when people have moved away.

Table 3 Determinants of Perceived Stress Scale (PSS-10) among study participants

Demographic	Type	PSS-10 score (mean ± SD)	*p* value*
Age (year)		$r = 0.325^{\#}$	0.005*
Gender	Male	15.97 ± 6.61	0.035*
	Female	19.03 ± 5.39	
Residence	Independent house	16.58 ± 6.08	0.097
	Apartment	20.29 ± 6.18	
	Hostel	18 ± 2.82	
Education	Less than high school	13 ± 6.52	0.003*
	High school	17.8 ± 7.79	
	Intermediate	16.5 ± 6.11	
	Graduate	18.52 ± 5.14	
	Post-graduate	22.62 ± 3.96	
Occupation	Student	16.32 ± 6.19	0.006*
	Employed	22.3 ± 3.36	
	Business	23.25 ± 5.56	
	Unemployed	15.83 ± 4.79	
Presence of any symptom over last 14 days	Yes	19.11 ± 5.11	0.4
	No	17.26 ± 6.33	
Satisfaction with available information	Yes	16.59 ± 6.33	0.038*
	No	22.67 ± 5.08	
	Do not know	19.5 ± 3.89	
Frequency of accessing information	Never	23 ± 4.24	0.074
	Occasionally	21 ± 3.69	
	Daily	16 ± 6.24	
	Multiple times a day	18.56 ± 6.16	
Knowledge of COVID-19 infection	Transmission score	$r = -0.149^{\#}$	0.194
	Prevention Score	$r = -0.089^{\#}$	0.438
	Symptom Score	$r = -0.085^{\#}$	0.462
Duration of type 1 diabetes (year)		$r = -0.042^{\#}$	0.717
Insulin regimen	Split mix regimen	19.70 ± 5.47	0.435
	Basal bolus	17.04 ± 6.13	
	Continuous infusion	18.40 ± 8.29	

* p value < 0.05 is considered significant

Spearman correlation

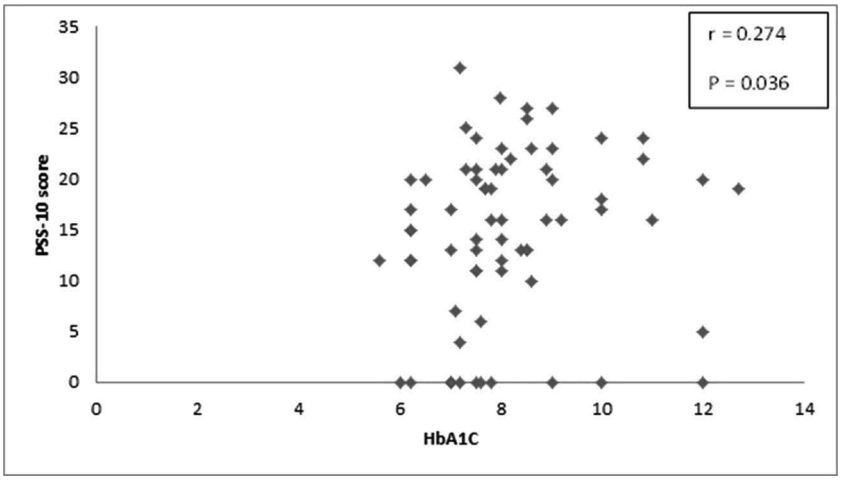

Fig. 1 Spearman correlation showing positive association of PSS-10 with HbA1C

Table 4 Challenges faced in diabetes management and potential solutions

	Participants *n* (%)
Reason for poor sugar control	
Difficulty in getting consultations	12 (9.6)
Difficulty in managing healthy diet	41 (33.06)
Lack of physical work	40 (32.25)
Unavailability of blood sugar monitoring strips	22 (17.74)
Unavailability of insulin	9 (7.25)
Potential solutions for better management	
Information on T1D care during COVID	46 (51.7)
Online consultations	58 (65.2)
Easy availability of insulin and glucometer strips	60 (67.4)

Discussion

The COVID-19 pandemic has emerged as a double trouble for those living with T1D. In an attempt to curb the spread of COVID-19, the Government of India announced a nationwide lockdown on 24th March 2020 by the PM [5]. This much needed step taken towards the containment of the virus has, to some extent, adversely affected the availability of routine health care facilities, supply of drugs, and medical equipment [6]. The limitation in access to health care facilities, drugs, and other resources, along with the known vulnerability to infection due to a compromised immune system, has left many with apprehension and increased stress levels [16].

In the present study, which was conducted just 5 weeks after the announcement of the nationwide lockdown, around 94.4% of the study participants reported low to moderate stress. The soaring stress level observed within the initial few weeks of the lockdown is an alarming finding in our study. Similar to the finding reported by Gao et al. [17], stress correlated positively with the age in our study. A better understanding of the impact of the pandemic, and professional uncertainty for an age group that either is planning or has recently started their career, could be a plausible explanation for this positive association. In agreement to previous epidemiological studies, which reported females to be at a higher risk for psychological disorders, we too noted that perceived stress was more among females compared with males [18, 19]. Similar to the findings reported by Du et al. [20], those with higher education were observed to have greater stress compared with their counterparts. This could possibly be attributed to their older age, or a result of apprehensions stemming from increased awareness regarding the pandemic, or both. In contradiction to increased stress reported among students by Wang et al. [19], we observed that salaried individuals perceived significantly more stress compared with students, self-employed or unemployed individuals. The uncertainty and potential negative impact on professional life could possibly explain the increased perception of stress among the salaried individuals.

All infectious outbreaks have their own unique set of characteristics in terms of mode of spread, type of illness caused, and preventive measures to be adopted. The fear of getting infected or infecting others is a common occurrence during the infectious pandemics. Provision of accurate health-related information to the masses is a crucial step in mitigating this fear and stress. A significantly higher PSS-10 score was seen among those who were reportedly dissatisfied with the available information. In contradiction to past studies [17], no difference in perceived stress was observed with the source of information. This could be because of smaller sample size in our study.

We observed a significantly higher PSS-10 score among those with poorly controlled diabetes, as reflected by the reported HBA1C within the preceding 3 months. This could be attributed to the fact that the current pandemic, possibly, augmented their pre-existing health-related stress. Previous reports have described the negative impact of stress on the medication adherence and disease outcome [21]. A similar trend was found in our study, where reduced frequency of SMBG was reported by the participants.

Stress and glycemic control have a bidirectional relationship. It can directly lead to disturbance in glucose regulation [22], or can indirectly lead to non-adherence to medication and healthy lifestyles [23]. We found that participants with a higher PSS-10 score reported worsened glycemic control on SMBG in the preceding 4 weeks. This is in contrast to other studies performed in developed countries that demonstrated no deterioration [24, 25], or even an improvement [26] in glycemic control during the lockdown period, attributed to improved self-care. This dissimilarity could possibly be attributed to the differences in the study population. Considering that India is an emerging economy, there is an expected difference in the availability of medical supplies and financial stability between patients.

Knowledge regarding preventive measures among the study group was remarkably good. This is in contrast to previous studies that have reported inadequate levels of knowledge about the measures of prevention towards the pandemic among the general public [27]. The positive trend in our study could be attributed to the vigorous measures taken by the government and the media to reinforce healthy practices and minimize misinformation. Also, most respondents in our study possessed at least high school level education and also suffered from an underlying chronic illness, thus likely to be more sensitized to such information. Unlike other studies [19, 20], we did not find any significant association of PSS-10 score with the level of knowledge towards COVID-19 transmission, prevention, and presentation.

Our study showed that majority of the participants obtained their information primarily through television and social media

sources. This is in agreement to previous studies which reported internet and television as prime sources of information during infectious outbreaks [28, 29]. As evident from our study, adolescents and young adults are observed to be more inclined towards the digital platforms; health authorities could utilize this resource to spread knowledge and awareness regarding the pandemic and also to provide psychological support to those at an increased risk of mental health-related issues.

People adopted different strategies to cope with stress during this outbreak. Sharing problems with friends and family members was the most common strategy adopted. This is similar to the findings reported in previous studies where participants reported increased need to talk with someone to vent out their distress [30].

Restricted mobility during the lockdown has compromised the care of T1D patients, due to disruption in follow-up visits, restricted availability of medicines, and other equipment. Majority of the study participants expressed the need for easy availability of insulin and glucometer strips as an indispensable measure to allay their stress. Telephonic or online consultations along with the provision of specific protocols for diabetes management during the COVID-19 were also suggested by around two-thirds of the respondents.

Limitations

Restriction of the study design to those with access to smartphones and English proficiency limits the extrapolation of results across all the sections of the society. Also, there could have been a response bias as the participants might have opted for the most socially acceptable responses. Furthermore, we used PSS-10, a subjective tool to assess mental health, and the results of this may not tally with the objective assessment tools. Similarly, in the absence of an objective assessment of physical activity and diet, impact of these two variables could not be analyzed on the glycemic control. But, given the current scenario of lockdown, remote collection of data using a self-reported online questionnaire was the most apt way to conduct this study. Glycemic control was assessed with SMBG, owing to the limitations in HbA1C testing during the times of the pandemic. Notwithstanding the above limitations, this study provides an invaluable information about the challenges faced by the individuals living with T1D, amidst the current pandemic. It provides a reference for further studies in this area. It highlights the need to formulate strategies to mitigate stress among those at risk, particularly when the difficulties are bound to increase due to the ongoing pandemic.

To conclude, we found that an increased prevalence of stress was seen among the Indian adolescents and young adults living with T1D. Female gender, salaried individuals, and pre-existing poorly controlled diabetes contributed to an increased risk of stress. Increased stress resulted in worsened glycemic control on SMBG. Amidst the focus of containing and defeating the disease, health care facilities might miss out on those with chronic illnesses, whose management may worsen during the pandemic.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants Yes.

Ethics committee approval Ethical clearance obtained.

Informed consent Obtained from every study participant prior to their participation in the survey.

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What is already known?

1. Infectious outbreaks are known to impact mental health adversely.
2. Those with chronic illnesses, like type 1 diabetes, are more vulnerable to psychological stress.

What this study adds?

1. Female gender, salaried individuals, and pre-existing poorly controlled diabetes contributed to an increased risk of stress.
2. Increased stress resulted in worsened glycemic control on SMBG.

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ORIGINAL ARTICLE

Diabetic retinopathy and its association with low glomerular filtration rate: a cross-sectional analysis of diabetes patients of community clinics across India

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Abstract

Aims To determine the prevalence of diabetic retinopathy (DR) in patients with T2DM having low estimated glomerular filtration rate (eGFR).

Methods A cross-sectional retrospective data analysis of T2DM patients' records who were screened for DR across Apollo Sugar Clinics from June 2016 to December 2016. DR was diagnosed through fundus examination; patients having eGFR values were grouped into eGFR < 60 and eGFR ≥ 60 mg/ml/1.73 m^2. Appropriate statistical tests were applied to identify the association of eGFR and DR, and significance was set at 2-tailed $p \leq 0.05$.

Results A total of 1547 T2DM patients were screened; mean (SD) age was 56.7 (10.0) years. Among them, data of 443 patients with eGFR were included in the analysis. Mean eGFR was 91.2 mg/ml/1.73 m^2; 12.5% patients had eGFR ≤ 60 mg/ml/1.73 m^2 and 87.5% had ≥ 60 mg/ml/1.73 m^2. DR was observed in 79 (17.8%) patients; it was higher in males (62%) than in females (38%). Further, the proportion of patients with DR was significantly higher in patients with eGFR ≤ 60 mg/ml/1.73 m^2 compared with that in patients with eGFR ≥ 60 mg/ml/1.73 m^2 (38% vs. 15%; $p < 0.001$).

Conclusion Association of DR with low eGFR in patients with T2DM may suggest presence of diabetes kidney disease in a community, thus reaffirming the significance of DR screening in community diabetes practices.

Keywords Diabetes · Eye · Complications · Glomerular filtration rate · Kidney · Retinopathy

Introduction

Diabetes mellitus, a global chronic disorder, affected 9.3% of South-East Asian adult population (20–79 years), a report by International Diabetes Federation (IDF) 2015, which is equivalent to 153 million people living with diabetes [1]. It is a condition that flags way for many complications if left untreated or if treatment is not appropriate. Type 2 diabetes mellitus (T2DM) and associated eye complications are a complex condition with multi-factorial etiology, where inherent genetic factors and triggering environmental factors play an active role [2]. Majority of the diabetes patients develop micro- or/and macrovascular complications with the increasing age, duration of disease, and poor glycemic control [3].

Diabetic retinopathy (DR) is one among the microvascular complications that contribute to other diabetes-related complications including nephropathy, peripheral neuropathy, and cardiovascular events [4–6]. In a report by Mottl et al., the risk factors associated with diabetes eye and kidney complications were similar as they share the same pathophysiology [5]. Of an estimated 285 million people globally, one-third of diabetes patients were expected to have vision-threatening eye diseases, specifically diabetes retinopathy (DR) or diabetes macular edema, over a period of time [3, 7, 8].

The risk of blindness in T2DM patients with DR is 25 times more than in non-diabetes individual [2]. Non-modifiable risk factors including duration of diabetes, residual beta-cell function, genetic predisposition, and insulin resistance and the

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modifiable risk factors including glycemic control, hypertension, nephropathy, hyperlipidemia, anemia, and obesity were some of the established risk factors for DR [2]. The two milestone trials United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Chronic Complications (DCCT) in the past have clearly demonstrated that achieving good glycemic control can delay the onset and progression of all diabetes-related microvascular complications including DR [9]. Therefore, for early detection, we sought to identify whether estimated glomerular filtration rate (eGFR) can serve as a predictive factor for eye complications in T2DM patients. The study purpose was to determine the prevalence of DR in T2DM patients with chronic kidney disease (CKD) stages 3 to 5 (GFR ≤ 60 ml/min per 1.73 m^2) and CKD stages 1 to 2 (GFR ≥ 60 ml/min per 1.73 m^2) attending community clinics across India.

Materials and methods

The present study was a retrospective analysis of 1547 T2DM patients registered at Apollo Sugar Clinics across India from January 2016 to November 2016. Apollo Sugar Clinics are spread across the nation having more than 35 clinics with over 90 health care providers. Diabetes patients aged above 18 years included in this analysis were suspected to have or potential for eye complication. The current study received ethics approval. At the time of clinic visit, patients were screened using fundus photography (non-dilated) for the diagnosis of DR complications (Fig. 1). The 3nethra fundus camera is used for imaging ocular disease DR. An experienced ophthalmologist graded the fundus images and diagnosed DR whether as non-proliferative diabetic retinopathy (NPDR) or as proliferative diabetic retinopathy (PDR).

Demographics and clinical details of the patients for the analysis were obtained from electronic medical records (EMR) and patient health records (PHR). At the time of clinic visit, patients' consent was obtained if they are willing to participate in the research activity. A total of 1547 patients were screened for the presence of any eye-related complications. eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and categorized into two CKD groups eGFR >60 and ≤ 60 mL/min/1.73 m^2 for analysis as mentioned in National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines (http://www2.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm).

Descriptive statistics was used to determine the prevalence of DR. Continuous variables were presented as mean (standard deviation) and median, categorical variables were presented as frequency and percentage. Statistical test chi-square was applied for categorical data to determine the significant difference in proportion patients with low eGFR and DR and analysis of variance (ANOVA) for continuous data to identify the association and or to identify the difference between the groups. Statistical analysis was done using SPSS version 20, with 2-tailed significance set at $p \leq 0.05$.

Results

A total of 1547 T2D were screened for DR complications; of these patients, 935 (60.4%) were males and 612 (39.6%) were females and the mean (SD) age was 56.7 (10.0) years. Among these patients, DR complication was observed in 204 (13.1%) patients. Though not significant, the percentage of male patients with DR was higher (122 [59.8%]) compared with that of female (82 [40.2%]) patients.

Of the total 1547 T2D patients, 443 patients having GFR were considered for the DR association. The mean eGFR was 91.2 (30.2) mg/ml/1.73 m^2; DR was observed in 79 (17.8%) patients; mean (SD) age was 55.5 (13.8) years; among them,

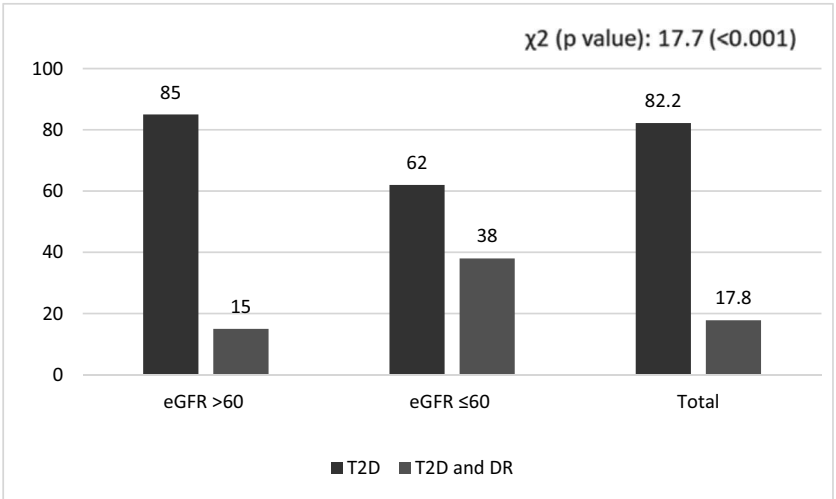

Fig. 1 Prevalence of DR in type 2 diabetes patients between subgroups of eGFR > 60 and ≤ 60 mg/ml/1.73 m^2

49 (62%) were males and 30 (38%) were females. The mean eGFR was significantly lower in patients with DR compared with that in patients without DR (79.4 vs. 93.8 mg/ml/1.73 m^2; $p = 0.000$). From the analysis, it was also observed that 388 (87.5%) diabetes patients had GFR > 60 mg/ml/1.73 m^2 and 55 (12.5%) patients had eGFR ≤ 60 mg/ml/1.73 m^2. Further to this analysis, the prevalence of DR in patients with GFR ≤ 60 was higher compared with that in patients with eGFR > 60 (38% vs. 15%; $p = 0.000$) (Fig. 2). There was also a significant correlation between low levels of eGFR (≤ 60 mg/ml/1.73 m^2) and DR. Although there was high preponderance of male diabetes patients, there was no significant gender variation with DR prevalence in both eGFR > 60 and eGFR ≤ 60 group patients.

Discussion

The current analysis demonstrates that 13.1% of T2DM patients were suffering from DR. Further, significantly higher proportion of patients with eGFR ≤ 60 mg/ml/1.73 m^2 were observed compared with patients with eGFR > 60 mg/ml/1.73 m^2.

Several studies have reported that hyperglycemia is the significant risk factor for eye complications, most importantly DR [2]. These complications increase the disease burden on diabetes patients and on the health care system. Early screening of complications and treatment to control blood glucose levels may contribute to preventing or reducing the disease burden in patients with diabetes.

Lee et al. reported that the prevalence of DR was higher in Western diabetes patients than in Asian diabetes patients [7]. Studies from the USA reported nearly 28.5–40.3% of patients with type 2 diabetes had DR [10, 11]. Similarly studies from Asian countries reported between 12.1 and 23.0% of patients having DR [12–15]. When compared with those of these studies, the prevalence of DR reported in our study is close to the Asian population. However, when compared with that in a study performed in the Singapore Indian ethnic group (30.4%) and urban India (18%), the prevalence reported here is very low (13.1%). This difference could be due to geographical heterogeneity, cultural variation, rapid urbanization, and change in lifestyle which may increase the chance of diabetes and associated complications [14, 16]. In 2012, A Meta-Analysis Study Group reported the 34.6% of patients with DR of any severity and the prevalence of proliferative diabetic retinopathy (PDR) is 6.96% [17]. Similarly different studies from India reported different prevalence rates [3]. A study from south India reported 34.1% of patients with DR, and a Chennai Urban Rural Epidemiology Study (CURES) reported 17.6% of diabetes patients with DR in urban population [16, 18]. A cross-sectional study by All India Ophthalmological Society reported 21.7%.of patients with DR in a predominantly urban set of patients and significantly more in male patients. Although our results are in line with respect to gender preponderance, it was not significantly enough.

Many studies have reported that eye complications are more common in patients with chronic kidney diseases (CKD) and more severe in patients with CKD stages 3 to 5 [19]. So far epidemiological studies have reported the prevalence of DR and CKD independently in diabetes patients, and to the best of our knowledge, the reports on the association of DR and CKD in diabetes patients are very rare. In a hospital-based study conducted by Wu et al., it was reported that eGFR is the significant risk factor for DR in patients with T2D and the eGFR levels were significantly low in DR patients compared with those in non-DR patients [20, 21]. Similarly present retrospective analysis also revealed significantly lower eGFR levels in DR patients compared with those in patients without DR (79.4 vs. 93.8 mg/ml/1.73 m^2; $p = 0.000$). Further, there was also a significant correlation between eGFR and DR, indicating low levels of eGFR may be a strong biomarker for DR. In addition to this, age was also significantly different between patients with DR and without DR (55.5 vs. 48.9 years). We also observed the prevalence of DR is significantly higher in patients with eGFR ≤ 60 mg/ml/1.73 m^2 than in patients with eGFR > 60 (38% vs. 15%; $p = 0.000$). Thus,

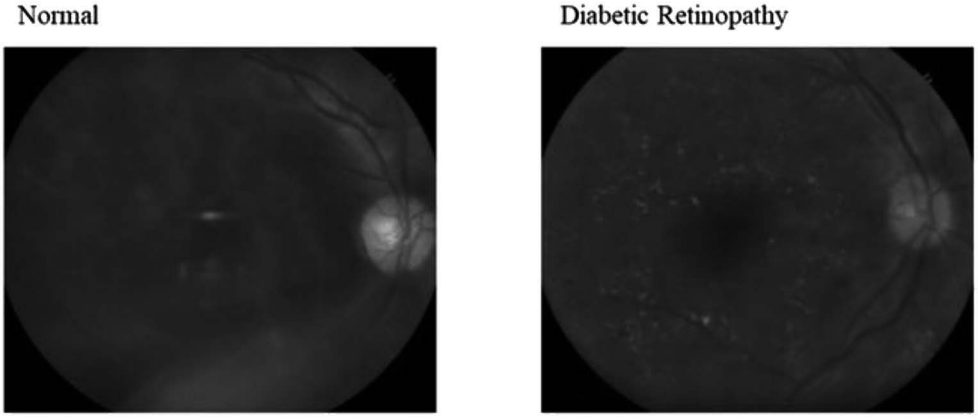

Fig. 2 Comparison of fundus images of normal and diabetic retinopathy patients

we noticed age and low eGFR ≤ 60 mg/ml/1.73 m^2 were observed to be highly significant risk factors for DR prevalence in diabetes patients. With the available evidence, more robust studies are underway to understand the early events in triggering eye complications, diagnostic markers, and treatment strategies in the management of diabetes patients.

Conclusions

The current study is one among the few studies from India that reports the prevalence of DR in T2DM patients from a community-based clinic diagnosed based on fundus photographs and correlating with eGFR, thus diabetes kidney disease (DKD). The association of eye disease with low GFR may suggest the presence of DKD in a community, thus restating the significance of early screening for eye complications in community-based diabetes practices. Therefore, implementing these real-time clinical observations into clinical decision pathways may improve the quality of health care delivery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Association of gestational diabetes mellitus with adverse pregnancy outcomes: our experience and meta-analysis

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Abstract

Aims/introduction The incidence of gestational diabetes mellitus (GDM) has increased recently worldwide with a subsequent occurrence of the associated adverse pregnancy outcomes. The objective of this study was to estimate the association between women with GDM and adverse pregnancy outcomes based on a cohort study and an integrated meta-analysis.

Materials and methods A retrospective cohort of 15,097 pregnant women (1718 GDM with 13,379 non-GDM controls) who delivered at two affiliated medical centers of Nantong University from Jan. 1, 2014 to Sep. 30, 2015, was conducted. Then, a meta-analysis was performed to explore and compare adverse pregnancy outcomes between GDM and non-GDM women.

Results In our cohort study, women with GDM were at significantly greater risk for cesarean section [crude relative risk (RR): 2.20, 95% confidence interval (CI): 1.97–2.44], macrosomia (crude RR: 2.36, 95% CI: 2.04–2.74) and large for gestational age (LGA) (crude RR: 2.03, 95% CI: 1.81–2.27), and a lower risk of low birth weight (LBW) (crude RR: 0.64, 95% CI: 0.47–0.86) and small for gestational age (SGA) (crude RR: 0.60, 95% CI: 0.45–0.80) than GDM-free women. However, the preterm birth incidence was not associated with GDM [crude RR: 1.08, 95% CI: 0.91–1.29]. Similarly, the meta-analysis including our cohort study also showed a significant association between GDM and preterm birth (pooled RR: 1.36, 95% CI: 1.26–1.48).

Conclusions Women with GDM still have an increased incidence of adverse pregnancy outcomes, which indicated that early prevention and clinical treatment of disease should be enhanced.

Keywords Cohort study · Gestational diabetes mellitus · Meta-analysis · Pregnancy outcomes

Yi Shen and Yulong Jia contributed equally to this work.

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Introduction

Gestational diabetes mellitus (GDM), one of the most common medical complications during pregnancy, presents an increasing prevalence of more than 35% around the world during the past decades [1]. However, according to the International Diabetes Federation (IDF) [2], the epidemiology of diabetes in pregnancy is still definitely unknown across many countries, concomitant with the disparity of diagnostic criteria [3]. The prevalence of GDM based on the former GDM criteria amounts to 2.9% in Japan, but the prevalence increased to 12% [4] when employing the International Association of the Diabetes and Pregnancy Study Groups criteria (IADPSG). A multicenter cohort study has reported that the incidence of GDM in Riyadh is 24.3% [5], which is two times higher than that of Japan. In addition, the incidence of GDM in China is approximately 17.5%, according to a representatively nationwide study covering 13 hospitals and 17,186 pregnant women [6].

GDM has emerged as an undoubtedly serious disease because of its overwhelmingly adverse perinatal outcomes, chronic placental insufficiency, preeclampsia, premature birth, and chronic hypoxia [7]. Compelling evidence has suggested that women with GDM history have sevenfold increased risk for developing T2D compared to non-GDM women. And approximately 50% of mothers with GDM would develop diabetes within 10 years, rendering GDM as one of the foremost predictors of T2D [8]. Collectively, women with GDM are more likely to present an increased risk for developing preeclampsia and gestational hypertensive disorders in their subsequent pregnancies and develop type 2 diabetes (T2D) across the long lifetime. Additionally, women with GDM are also at increased risk of delivering large for gestational age infant (LGA), and furthermore likely to be delivered by cesarean and/or suffer birth injury [9]. Long-term adverse outcomes on the offspring include obesity and abnormal glucose metabolism during future life [10, 11].

There have been few studies on pregnancy outcomes for women with GDM in China and that previous studies especially focus on the coverage of Beijing [12, 13]. Traditional recognition of pregnancy health is quite unique in China, and there are apparently diverse lifestyles in different regions. In the meantime, with the enormous change of diet patterns and lifestyles for general population, there is still a scarcity of comprehensive profiles for examining the impact of GDM on perinatal outcomes in China. Therefore, a hospital-based retrospective cohort study in Jiangsu, China, was performed to explore the adverse events of the maternal and the offspring. Furthermore, considering the diversity and complexity of adverse events, a meta-analysis was conducted to summarize the evidence of perinatal GDM adverse outcomes, including this special longitudinal study.

Materials and methods

Participants and study design

A retrospective cohort study was conducted to explore the impact of GDM on perinatal outcomes. The participants were recruited from those women who delivered at two affiliated medical centers of Nantong University (the Affiliated Hospital of Nantong University (AHNU) and the Nantong Maternal and Child Health Hospital (NMCHH)), in Jiangsu Province, from Jan. 1, 2014 to Sep. 30, 2015. Basic informations on demographic characteristics, clinical symptoms, and perinatal outcomes were collected individually from computer-assisted medical record systems in these two hospitals. Women with diabetes before pregnancy, and/or with a fetus or a newborn having confirmed chromosomal aberrations and/or genetic syndromes, were excluded. All the pregnant women were routinely screened for GDM at 26–28 weeks' gestation. GDM was diagnosed if the fasting plasma glucose (FPG) met at least one of the following criteria: (i) FPG is more than 5.1 mmol/L; (ii) 1-h plasma glucose was more than 10.0 mmol/L; (iii) 2-h plasma glucose is more than 8.5 mmol/L by 75 g oral glucose tolerance testing. Pre-delivery body mass index (PBMI) was calculated through self-reported pre-delivery weight/height (kg/m^2). Gestational hypertension was defined as new onset of elevated blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on at least two occasions 6 h apart) after 20 weeks of gestation in a previously normotensive woman.

The main outcomes of all the eligible women were collected. Maternal outcomes included cesarean section, preterm (< 37w) and stillbirth (after 20 completed gestational weeks). Neonatal outcomes for live births in singleton pregnancy included macrosomia (birth weight ≥ 4000 g), low birth weight (LBW, birth weight < 2500 g), LGA (birth weight > 90th percentile), small for gestational age (SGA, birth weight < 10th percentile), and Apgar score at 5 min < 7.

Meta-analysis

The meta-analysis was conducted following the PRISMA extension statement. We systematically searched electronic database including PubMed, Embase, and Cochrane Library based on the logic combination of keywords and text words associated with GDM and adverse pregnancy outcomes from Jan.1, 2000 to Mar. 31, 2018 (Table S1). Additional eligible articles were manually searched for those included studies. Experimental studies (randomized and non-randomized) and observational studies (cross-sectional, prospective/retrospective cohort and case-control) with maternal outcomes (cesarean section, preterm birth and stillbirth) and neonatal outcomes (macrosomia, LBW, LGA, SGA, and Apgar score at 5 min < 7) of mothers with GDM during pregnancy were considered and further evaluated. The included studies must report relative risks (RRs) and 95% confidence intervals (CIs), or such critical information could be derived. Data were independently extracted by two authors (Y.L.J and J.Z.) by the standardized form. Any controversy was settled by the third author (Y.S.). The Newcastle-Ottawa quality-assessment scale (NOS) and Agency for Healthcare Research and Quality (AHRQ) were employed to assess the quality of those included studies.

Statistical analysis

Comparison of continuous variables was done by *t* test, while χ^2 test or *Fisher's* exact probability was used for categorical variables. Logistic regression analysis was used to estimate associations between women with GDM and adverse pregnancy outcomes. RRs and 95% CIs were computed. $p \leq 0.05$ was considered as statistically significant. The statistical analyses were conducted with IBM SPSS Statistics Software (21.0, Armonk, NY, USA).

Meta-analyses were conducted by selecting random effects model or fixed effects model according to I^2 statistic, an indicator calculated to quantify the proportion of the total variation owing to the heterogeneity. Besides, publication bias was checked by the funnel plots and tested with Egger's test. A sensitivity analysis was performed using the leave-one-out approach to analyze sources of heterogeneity across the studies. Stata 13.0 software (StataCorp, U.S.) was used to perform meta-analyses.

Results

Cohort study

Participant characteristics

A total of 15,097 women were qualified for this cohort, out of which 1718 were diagnosed with GDM and 13,379 delivered at the same gestational period, but without known GDM. Table 1 shows the basic characteristics of included GDM and non-GDM groups in our cohort study. The mean age of GDM group was significantly older than non-GDM group and older mothers (≥ 35 years) were 227 accounting for 13.21%, almost two times higher than non-GDM group (6.16%). The PBMI of the GDM group and control groups were 28.54 ± 3.88 and 27.14 ± 3.38 kg/m^2, respectively ($p < 0.001$). The gestation age of GDM group was significantly smaller than non-GDM group, while the gestation rate within 39 weeks was 44.76% vs. 41.89% ($p < 0.05$). The incidence of gestational hypertension was significantly higher in GDM group (2.56%) than that in control group (1.68%). 16.59% of GDM women own the history of previous abortion, while only 9.90% were found in non-GDM group ($p < 0.001$). The proportion of in vitro fertilization (IVF) in GDM group (1.51%) was also two times higher than that in non-GDM (0.72%, $p < 0.05$).

Adverse pregnancy outcomes

The pregnancy outcomes are listed in Table 2. The rate of cesarean section was significantly higher in GDM group than that in non-GDM group (68.45% vs. 49.71%, $p < 0.001$), while no significant differences were found in the incidence of preterm birth and stillbirth respectively. In view of the neonates, a total of 13,787 live births in singleton pregnancies were qualified during the study period, 1669 in GDM group and 12,118 in non-GDM group, respectively. GDM group had a higher risk of macrosomia (crude RR: 2.36) and LGA (crude RR: 2.03), and a lower risk of LBW (crude RR: 0.64) and SGA (crude RR: 0.60) than in non-GDM group. There were no significant differences in terms of incidences of Apgar at 5 min < 7 between two groups.

Meta-analysis

Characteristics and quality of the included studies

Sixty-three studies involving 1,545,464 participants and 252,676 women with GDM were ultimately included in the meta-analysis [12–74]. Figure 1 shows the flow chart that summarizes the process of identifying these studies. Tables 3 and 4 provided detailed information of the included study. Most of the studies were of cohort design, seven studies [15, 18, 22, 25, 33, 67, 68] were of case control design and four studies [38, 60, 65, 69] were of cross-sectional design. According to the NOS system and AHRQ, the scores of all studies were ≥ 5, which denoted good quality.

Adverse pregnancy outcomes

Figure 2 suggested that a significantly positive association between GDM and cesarean section existed ($n = 52$ studies; pooled RR: 1.45, 95% CI: 1.41–1.50; $I^2 = 92.3\%$). Meanwhile, the preterm birth rate was significantly higher in the GDM group than the non-GDM group ($n = 33$; pooled RR: 1.36, 95% CI: 1.26–1.48; $I^2 = 92.3\%$) (Fig. 3). The pooled RR presented a nonsignificant association between GDM and stillbirth (pooled RR: 1.15, 95% CI: 0.68–1.94; $I^2 = 89.8\%$) (Fig. S1).

A significantly positive relationship between GDM and macrosomia was established ($n = 37$; pooled RR: 1.80, 95% CI: 1.61–2.01; $I^2 = 93.3\%$) (Fig. 4). Consistently, 30 studies showed that the potential risk with LGA was 1.83 (95% CI: 1.56–2.15; $I^2 = 98.2\%$) (Fig. 5). However, GDM was non significantly associated with LBW (pooled RR: 0.87, 95% CI: 0.74–1.03; $I^2 = 65.0\%$), SGA (pooled RR: 0.85, 95% CI: 0.71–1.01; $I^2 = 84.3\%$) and Apgar at 5 min < 7 (pooled RR: 1.15, 95% CI: 0.96–1.37; $I^2 = 60.0\%$) (Fig. S2-S4).

Sensitivity analysis

The results of sensitivity analysis using leave-one-out approach were shown in Fig. S5-S12. None of the individual studies influenced the originally total results.

Publication bias

As shown in funnel plot, there was no obvious publication bias among all the analyses of GDM and adverse pregnancy outcomes (Fig. S13-S20).

Table 1 Basic characteristics of participants

Characteristic	GDM ($n = 1718$)	Nondiabetic ($n = 13,379$)	p
Maternal age (y)	28.98 ± 4.50	27.08 ± 4.10	< 0.001
< 35	1491 (86.79)	12,555 (93.84)	< 0.001
≥ 35	227 (13.21)	824 (6.16)	
Pre- delivery BMI (kg/m^2)	28.54 ± 3.88	27.14 ± 3.38	< 0.001
Completed weeks' gestation (wk)	38.85 ± 1.67	39.02 ± 1.80	< 0.001
<39	769 (44.76)	5605 (41.89)	0.023
≥ 39	949 (55.24)	7774 (58.11)	
Weight of neonates (g)	3476.34 ± 536.63	3321.82 ± 489.79	< 0.001
Gestational hypertension			
No	1674 (97.44)	13,154 (98.32)	0.009
Yes	44 (2.56)	225 (1.68)	
City			
No	650 (37.83)	4986 (37.27)	0.647
Yes	1068 (62.17)	8393 (62.73)	
Nullipara			
No	523 (30.44)	3397 (25.39)	< 0.001
Yes	1195 (69.56)	9982 (74.61)	
Previous abortion			
0	1433 (83.41)	12,054 (90.10)	< 0.001
1	199 (11.58)	898 (6.71)	
≥ 2	86 (5.01)	427 (3.19)	
Previous preterm birth			
0	1690 (98.37)	13,202 (98.68)	0.486
1	28 (1.63)	175 (1.31)	
≥ 2	0 (0)	2 (0.01)	
Plurality			
1	1670 (97.21)	13,044 (97.50)	0.472
≥ 2	48 (2.79)	335 (2.50)	
IVF			
No	1692 (98.49)	13,283 (99.28)	0.001
Yes	26 (1.51)	96 (0.72)	

Values are given as mean ± SD or number (percentage)

GDM, gestational diabetes mellitus; *BMI*, body mass index; *IVF*, in vitro fertilization

Discussion

Women with GDM still presented an elevated trend and complicated patterns nationwide and worldwide, and perinatal healthcare still remains a serious health problem. The incidence of GDM has increased recently worldwide with a subsequent occurrence of the associated adverse pregnancy outcomes. To the best of our knowledge, this is the first retrospective cohort design focus on the association between GDM and the risk of adverse pregnancy outcomes in Jiangsu, China. The objective was to estimate the association between women with GDM and adverse pregnancy outcomes based on a cohort study and an integrated meta-analysis.

Our study suggests that women with GDM possess a definitely increased risk for cesarean section, while no significant association is detected on the risk of preterm birth and stillbirth. And, offsprings of GDM have an increased risk of macrosomia and LGA, while presenting a decreased risk of LBW and SGA. Additionally, due to the lack of systematically synthesized data on the association between GDM and adverse pregnancy outcomes, a meta-analysis including our cohort study has been conducted to summarize the adverse effects of GDM on obstetrical and neonatal outcomes.

Undoubtedly, maternal age and obesity are definitely associated with adverse pregnancy outcomes. Previous studies showed an increasing prevalence of GDM concomitant with

Table 2 Comparison of the adverse pregnancy outcomes between gestational diabetes groups and controls

Outcome	GDM ($n = 1718$)	Nondiabetic ($n = 13,379$)	p	RR (95% CI)	Adjusted RR (95% CI)[‡]	Adjusted RR (95% CI)[§]	Adjusted RR (95% CI)	Adjusted RR (95% CI)
Maternal outcome, n (%)								
Cesarean section	1176 (68.45)	6651 (49.71)	< 0.001	2.20 (1.97–2.44)	1.96 (1.76–2.19)	2.19 (1.96–2.43)	2.02 (1.81–2.25)[¶]	1.83 (1.64–2.05)[‡‡]
Preterm birth	160 (9.31)	1160 (8.67)	0.375	1.08 (0.91–1.29)	1.07 (0.90–1.27)	1.06 (0.89–1.26)	1.04 (0.88–1.24)[¶]	1.02 (0.85–1.22)[‡‡]
Stillbirth	2 (0.12)	9 (0.07)	0.814	1.73 (0.37–8.02)	1.86 (0.40–8.64)	1.67 (0.36–7.76)	1.50 (0.32–7.13)[¶]	1.55 (0.32–7.56)[‡‡]
Neonatal outcome[†], *n* (%)								
Macrosomia	265 (15.88)	897 (7.40)	< 0.001	2.36 (2.04–2.74)	1.89 (1.62–2.20)	2.36 (2.04–2.74)	2.50 (2.15–2.90)[††]	1.99 (1.71–2.33)[§§]
LBW	49 (2.94)	549 (4.53)	0.003	0.64 (0.47–0.86)	0.69 (0.51–0.93)	0.60 (0.45–0.81)	0.52 (0.39–0.71)[††]	0.38 (0.27–0.54)[§§]
LGA	551 (33.01)	2370 (19.56)	< 0.001	2.03 (1.81–2.27)	1.69 (1.50–1.90)	2.03 (1.82–2.27)	2.07 (1.85–2.32)[††]	1.73 (1.54–1.94)[§§]
SGA	52 (3.12)	616 (5.08)	< 0.001	0.60 (0.45–0.80)	0.67 (0.50–0.90)	0.58 (0.43–0.77)	0.58 (0.43–0.77)[††]	0.63 (0.47–0.84)[§§]
Apgar at 5 min < 7	8 (0.48)	84 (0.69)	0.314	0.69 (0.33–1.43)	0.68 (0.33–1.42)	0.65 (0.31–1.35)	0.50 (0.24–1.05)[††]	0.48 (0.23–1.02)[§§]

[†] Live births in singleton pregnancy; GDM ($n = 1669$), Nondiabetic ($n = 12,118$)

[‡] Adjusted RR for pre- delivery BMI

[§] Adjusted RR for gestational hypertension

[¶] Adjusted RR for maternal age

[††] Adjusted RR for completed weeks' gestation

[‡‡] Adjusted RR for pre- delivery BMI, gestational hypertension and maternal age

[§§] Adjusted RR for pre- delivery BMI, gestational hypertension and completed weeks' gestation

GDM, gestational diabetes mellitus; *RR*, relative risk; *CI*, confidence interval; *LBW*, low birth weight; *LGA*, large for gestational age; *SGA*, small for gestational age; *BMI*, body mass index

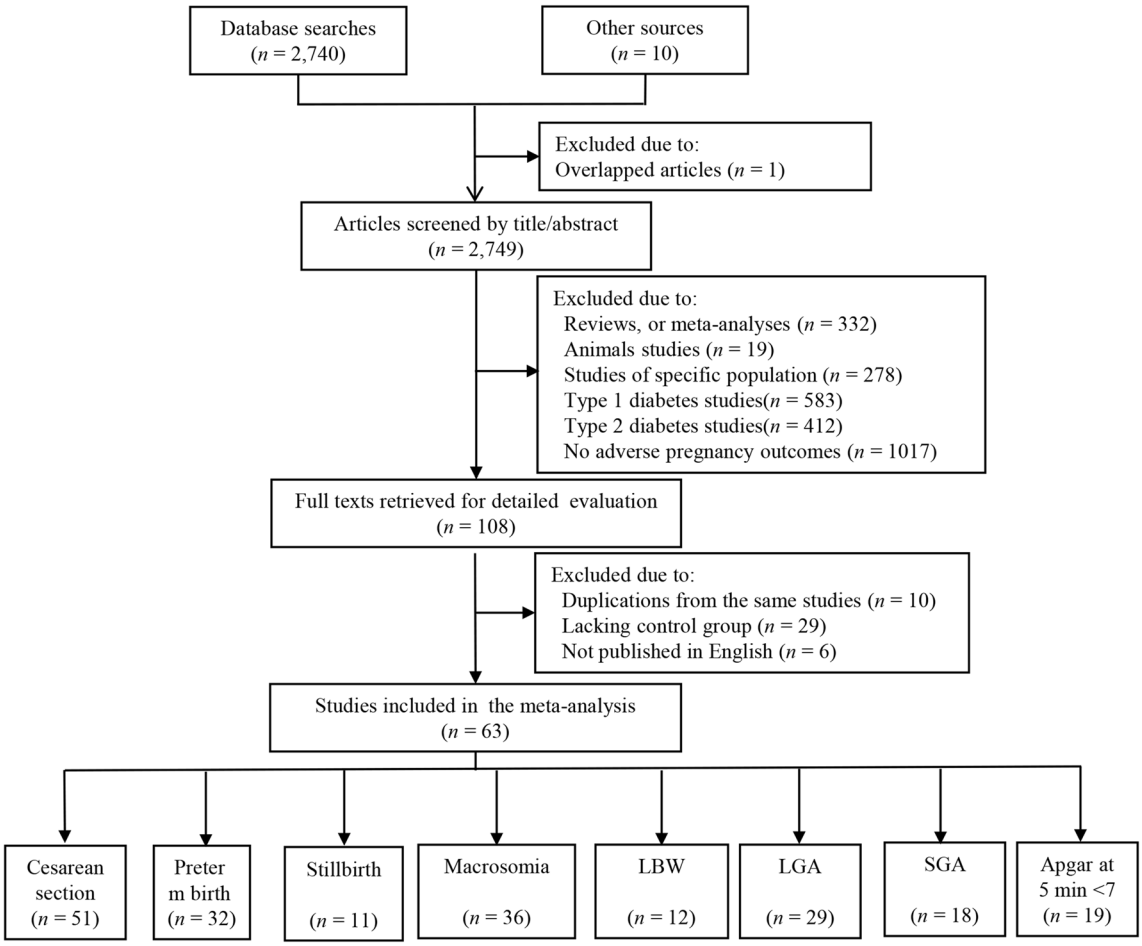

Fig. 1 Flow diagram of search results. LBW, low birth weight; LGA, large for gestational age; SGA, small for gestational age

advanced maternal ages [73]. And the mean gestational age at delivery was significantly different in the two groups in our cohort study. This could be explained by the declining ability to regulate glucose metabolism and body function with the increase of maternal age. A meta-analysis reported that obese pregnant women are 2.1–8.5 times more likely to develop GDM than normal-weight pregnant women [75]. A study showed that obesity was an important independent predictor of LGA than maternal hyperglycemia [76]. PBMI is considered as the main confounding factor because the combination of GDM and obesity presents an enhancive impact on pregnancy outcomes. It is difficult to identify the direct effect of GDM and/or the conjoint effect of GDM and gestational hypertension on the overall pregnancy outcomes, although several studies suggest that GDM is the primary risk factor of gestational hypertension [73]. Giving that both conditions often occur simultaneously, we calculated the RRs with adjustment for maternal age, PBMI, gestational age, and gestational hypertension.

The results in our cohort study suggest the independently significant effect of GDM for cesarean section exists, which is also consistent with our meta-analysis. Women with GDM were more likely to deliver by cesarean section than nondiabetic pregnancies. This ascending tendency might be associated with the increased rate of macrosomia among women with GDM [77]. Whereas, our cohort results present a nonsignificant increase for the preterm birth between GDM and non-GDM, which were contrary to the pooled outcome in the meta-analysis. The inconsistent findings could be partially attributable to variations of study population, the potential threshold effect of maternal glycemia, the definition of spontaneous preterm delivery, and both maternal and fetal indications (preeclampsia, etc.) [78]. Stillbirth in GDM has been a well-recognized complication, while the incidence has decreased due to clinical protocols for screening, treatment, and antenatal surveillance of patients [79]. A retrospective cohort study, including 4,190,953 non-anomalous deliveries and 193,028 deliveries to women with GDM, reported the overall prevalence of stillbirth in GDM group was 1.71‰ [80]. In our cohort study, the nonsignificant association between stillbirth and GDM might be because of its relatively low incidence in both GDM and non-GDM group (1.16 vs. 0.67‰).

Collectively, the outcome of fetal development for GDM is characterized by increased size and weight

Table 3 Publication characteristics of the included studies in this meta-analysis

First author (year)	Country	No. of centers	Design	Period of study	Grade	No. of population	
						GDM	Nondiabetic
Griffin ME (2000) [14]	Ireland	1	Cohort	NA	5	35	3090
Sobande AA (2000) [15]	Saudi Arabia	1	Case-control	1991.01–1992.12	4	57	83
Svare JA (2001) [16]	Denmark	1	Cohort	1996.02–2000.11	5	327	295
Jimenez-M JJ (2002) [17]	Spain	1	Cohort	1995	4	65	1666
Moore TR (2002) [18]	America	1	Case-control	1994.01.01–2000.03.01	5	218	590
Bo S (2003) [19]	Italy	1	Cohort	1999.04–2001.02	6	133	333
Catalano PM (2003) [20]	America	1	Cohort	1990–2000	6	195	220
Jensen DM (2003) [21]	Denmark	4	Cohort	1992.01.01–1996.12.31	5	97	2596
Loukovaara M (2004) [22]	Finland	1	Case-control	2000.07–2002.04	5	25	56
Keshavarz M (2005) [23]	Iran	1	Cohort	1999.12–2001.01	6	63	1247
Langer O (2005) [24]	America	Multicenter	Cohort	1990.01–1999.09	7	555	1110
Loukovaara M (2005) [25]	Finland	1	Case-control	2000.06–2002.05	5	28	62
Berg M (2007) [26]	Sweden	1	Cohort	1998.07.01–2002.06.30	5	719	30,823
Suhonen L (2008) [27]	Finland	1	Cohort	1988–1997	5	520	805
Lin CH (2009) [28]	Taiwan, China	1	Cohort	2001.03–2006.02	4	617	1250
Segregur J (2009) [29]	Croatia	1	Cohort	1995–2003	4	351	1502
Fadl HE (2010) [30]	Sweden	Multicenter	Cohort	1991–2003	6	10,525	1,249,772
Lawlor DA (2010) [31]	England	Multicenter	Cohort	1991.04.01–1992.12.31	7	53	10,126
Bener A (2011) [32]	Qatari	1	Cohort	2010.01–2011.04	6	262	1346
Bhat M (2012) [33]	India	1	Case-control	2007.08–2008.06	4	286	292
Gorgal R (2012) [34]	Portugal	1	Cohort	2004.01–2007.11	5	220	660
Gasim T (2012) [35]	Saudi Arabia	1	Cohort	2001.01–2008.12	4	220	220
Eslamian L (2013) [36]	Iran	1	Cohort	2011.03–2012.05	4	112	159
Wahabi HA (2013) [37]	Saudi Arabia	1	Cohort	2010.01.01–2010.12.31	5	569	2472
Bhorat IE (2014) [38]	South Africa	1	Cross-sectional	2012.11–2013.07	4	29	29
Okby R (2014) [39]	Israel	1	Cohort	1988.01.01–2010.12.31	5	341	4055
Wahabi HA (2014) [40]	Saudi Arabia	1	Cohort	2011.07.01–2012.06.30	5	415	2286
Kaul P (2015) [41]	Canada	Multicenter	Cohort	1999.04–2010.03	6	7332	213,765
Kgosidialwa O (2015) [42]	Ireland	5	Cohort	2009.09–2013.08	7	567	2499
Ogonowski J (2015) [43]	Poland	1	Cohort	2009.01–2011.12	5	519	766
Ovesen PG (2015) [44]	Denmark	Multicenter	Cohort	2004.01.01–2010.06.30	5	9014	389,609
Pintaudi B (2015) [45]	taly	Multicenter	Cohort	2002.01.01–2010.12.31	7	3851	11,553
Sacks DA (2015) [46]	California	1	Cohort	2005.10.30–2010.12.30	6	1892	7943
Srichumchit S (2015) [47]	Thailand	1	Cohort	2002.01.01–2012.12.31	6	1350	20,421
Vilmi-Kerala T (2015) [48]	Finland	1	Cohort	2011.08–2014.07	5	120	120
Wang LF (2015) [12]	China	1	Cohort	2012–2013	5	587	478
Aviram A (2016) [49]	Israel	1	Cohort	2009–2014	5	132	1717
Berglund SK (2016) [50]	Spain	Multicenter	Cohort	2008–2012	5	76	128
Cosson E (2016) [51]	France	1	Cohort	2002.1–2010.12	5	2097	13,436
Hilden K (2016) [52]	Sweden	Multicenter	Cohort	1998–2012	6	4114	790,228
Lai FY (2016) [53]	Canada	Multicenter	Cohort	2005–2011	6	18,137	306,576
Lu MC (2016) [54]	Taiwan, China	1	Cohort	2006.03–2013.01	5	457	9002
Nguyen TH (2016) [55]	Canada	1	Cohort	2005.04.01–2009.03.31, 2011	4	1827	1885
Peixoto AB (2016) [56]	Brazil	1	Cohort	2012.02–2015.03	4	56	684
Tward C (2016) [57]	Canada	1	Cohort	2003.10–2014.12	6	89	1021
Anand SS (2017) [58]	Canada	Multicenter	Cohort	2011.07.11–2015.11.10	4	365	641
Beka Q (2017) [59]	Canada	Multicenter	Cohort	2000.04.01–2009.03.31	5	12,140	314,583
Billionnet C (2017) [60]	France	Multicenter	Cross-sectional	2012	6	57,629	735,519
Bogdanet D (2017) [61]	Ireland	Multicenter	Cohort	2009–2013	6	752	2496
Bricelj K (2017) [62]	Slovenia	Multicenter	Cohort	2003–2012	5	363	7400
Egan AM (2017) [63]	Europe	11	Cohort	2012.01–2014.02	7	153	628
Feng H (2017) [13]	China	15	Cohort	2013.6.20–2013.11.30	6	2927	11,814
Jiang S (2017) [64]	Australia	1	Cohort	2011.01–2015.04	5	94	3185
Koivunen S (2017) [65]	Finland	Multicenter	Cross-sectional	2010	5	6679	52,386
Lauring JR (2017) [66]	America	1	Cohort	2012.04.01–2013.03.31, 2014	5	36	2655
Liao S (2017) [67]	New Zealand	Multicenter	Case-control	2004.11–2007.10	4	28	28
Lobmaier SM (2017) [68]	Germany	1	Case-control	2014.09–2015.06	5	58	58
Metcalfe A (2017) [69]	Canada	Multicenter	Cross-sectional	2004.04.01–2015.03.31	5	149,780	2,688,231
Mortier I (2017) [70]	France	1	Cohort	2011.01.01–2012.07.31	5	60	384
Rosen H (2017) [71]	Israel	1	Cohort	2007.01.01–2014.12.31	6	1883	38,635
Vally F (2017) [72]	Australia	1	Cohort	2014	5	202	202
Wahabi H (2017) [73]	Saudi Arabia	Multicenter	Cohort	2013–2015	5	2354	6951
Yan Y (2017) [74]	China	1	Cohort	2009.01.01–2011.12.31	5	92	1475
Ours	China	2	Cohort	2014.01.01–2015.09.30		1718	13,379

GDM, gestational diabetes mellitus; *NA*, not available

Table 4 Demographic characteristics of the included studies in this meta-analysis

First author (year)	Maternal age†		Completed weeks' gestation†		Pregestational BMI†		Nullipara, *n*		Birth weight†	
	GDM	Nondiabetic	GDM	Nondiabetic	GDM	Nondiabetic	GDM	Nondiabetic	GDM	Nondiabetic
Griffin ME (2000) [14]	31.0 ± 5.6	27.0 ± 5.7	NA	NA	NA	NA	10	1163	NA	NA
Sobande AA (2000) [15]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Svare JA (2001) [16]	31.9 ± 5.7	29.8 ± 5.3	39.1 ± 1.7	39.8 ± 2.0	28.4 ± 5.8	26.6 ± 4.9	94	105	3593 ± 597	3507 ± 576
Jimenez-Moleon JJ (2002) [17]	31.3 ± 4.8	28.5 ± 4.8	38.8 ± 1.6	39.2 ± 1.8	26.9 ± 5.8	23.4 ± 3.4	NA	NA	3384 ± 561	3253 ± 490
Moore TR (2002) [18]	32.0 ± 8.0	29.8 ± 6.6	37.3 ± 2.5	36.8 ± 2.6	NA	NA	63	207	3448 ± 820	2918 ± 735
Bo S (2003) [19]	32.9 ± 4.8	31.7 ± 4.2	38.7 ± 2.1	39.0 ± 1.7	21.5 ± 2.0	21.2 ± 1.9	83	212	3186 ± 578	3271 ± 446
Catalano PM (2003) [20]	29.0 ± 6.1	28.0 ± 5.8	38.4 ± 1.3	39.0 ± 1.4	NA	NA	121	137	3398 ± 550	3337 ± 549
Jensen DM (2003) [21]	31.9 (28.7–35.0)	29.8 (26.6–33.5)	39 (37.9–39.9)	40.3 (39.1–41.1)	27.0 (24.2–32.1)	25.8 (21.8–30.0)	34	1227	3590 (3260–4050)	3600 (3250–4000)
Loukovaara M (2004) [22]	35.5 ± 0.16	31.2 ± 0.08	263 ± 0.4	279 ± 0.13	30.5 ± 0.24	22.1 ± 0.07	6	25	3612 ± 19.4	3781 ± 14.70
Keshavarz M (2005) [23]	30 ± 5.2	25.9 ± 5.4	38.7 ± 1	39.4 ± 1.4	29.2 ± 4.7	24.9 ± 4.5	NA	NA	NA	NA
Langer O (2005) [24]	27.6 ± 6	25.0 ± 6	39.0 ± 2.0	39.1 ± 2.1	NA	NA	122	233	3600 ± 540	3312 ± 601
Loukovaara M (2005) [25]	35.4 ± 0.15	31.2 ± 0.08	263 ± 0.19	279 ± 0.13	30.6 ± 0.21	22.3 ± 0.06	7	26	3713 ± 20.22	3741 ± 9.27
Berg M (2007) [26]	31.9 ± 5.0	30.1 ± 5.0	39.3 ± 1.8	39.1 ± 2.2	27.1 ± 9.1	24.1 ± 4.0	NA	NA	3460.3 ± 603.1	3472.6 ± 619.7
Suhonen L (2008) [27]	33.5 ± 5.4	29.5 ± 5.0	39.6 ± 1.6	39.7 ± 1.9	26.1 ± 5.4	23.1 ± 3.9	187	332	3616 ± 580	3517 ± 570
Lin CH (2009) [28]	33.7 ± 4.1	32.2 ± 4.1	NA	NA	NA	NA	NA	NA	3265.3 ± 491.6	3194.2 ± 425.9
Segregur J (2009) [29]	31.56 ± 5.73	28.19 ± 5.19	39.63 ± 1.98	39.33 ± 2.14	NA	NA	NA	NA	3506.6 ± 732.7	3350.2 ± 585.1
Fadl HE (2010) [30]	31 ± 5.3	29 ± 5.0	NA	NA	27.7 ± 5.9	24.0 ± 4.1	3537	531,153	NA	NA
Lawlor DA (2010) [31]	29.7 ± 5.0	28.2 ± 4.9	38.2 ± 1.9	39.5 ± 1.9	26.6 ± 6.4	22.9 ± 3.8	NA	NA	3711 ± 655	3416 ± 536
Bener A (2011) [32]	33.4 ± 6.5	31.9 ± 6.3	NA	NA	NA	NA	NA	NA	NA	NA
Bhat M (2012) [33]	26.63 ± 4.547	26.43 ± 4.412	NA	NA	NA	NA	NA	NA	NA	NA
Gorgal R (2012) [34]	32.8 ± 5.1	29.0 ± 5.6	38.9 ± 0.9	39.3 ± 1.0	26.5 ± 5.0	23.3 ± 4.1	NA	NA	3256.6 ± 421.1	3265.9 ± 416.1
Gasim T (2012) [35]	32.4 ± 7.5	33.2 ± 6.8	38.6 ± 1.4	39.4 ± 1.6	27.4 ± 1.4	27.2 ± 1.5	34	36	3545 ± 466	3356 ± 332
Eslamian L (2013) [36]	27.23 ± 4.19	25.48 ± 4.06	37.72 ± 1.7	39.36 ± 1.33	26.59 ± 3.6	23.98 ± 2.6	NA	NA	3336.07 ± 630	3259.75 ± 490
Wahabi HA (2013) [37]	32.40 ± 5.89	28.62 ± 5.98	NA	NA	NA	NA	NA	NA	3197.60 ± 556.67	3120.14 ± 578.18
Bhorat IE (2014) [38]	32 (30–33)	32 (30–33)	38.35 (37.7–38.7)	39.43 (39–39.71)	NA	NA	NA	NA	3310 (3586–3850)	2910 (2965–3017)
Okby R (2014) [39]	32.05 ± 5.6	29.58 ± 5.5	35.57 ± 2.5	35.39 ± 3.2	NA	NA	113	1156	2320	2245
Wahabi HA (2014) [40]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kaul P (2015) [41]	31.9 ± 5.5	28.6 ± 5.6	NA	NA	NA	NA	4135	137,623	3311 ± 574	3344 ± 586
Kgosidialwa O (2015) [42]	33.4 ± 4.9	31.5 ± 5.2	39.3 ± 1.8	39.9 ± 1.7	30.5 ± 6.1	26.7 ± 4.8	251	1098	3.4 ± 0.6	3.6 ± 0.6
Ogonowski J (2015) [43]	30.71 ± 4.5	29.32 ± 4.8	NA	NA	24.51 ± 4.9	22.90 ± 4.0	281	452	3310.5 ± 496.2	3305.7 ± 508.9
Ovesen PG (2015) [44]	32.5 ± 5.0	30.7 ± 4.8	38.9 ± 1.7	39.8 ± 1.8	29.1 ± 6.4	24.1 ± 4.8	3552	171,818	3519 ± 566	3523 ± 562
Pintaudi B (2015) [45]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sacks DA (2015) [46]	NA	28.4 ± 5.9	NA	39.0 ± 1.7	NA	NA	731	3640	NA	3333.8 ± 509.9
Srichumchit S (2015) [47]	32.57 ± 5.29	27.39 ± 7.04	37.7 ± 2.6	37.8 ± 3.0	NA	NA	586	11,829	3024.2 ± 607.2	2941.7 ± 590.4
Vilmi-Kerala T (2015) [48]	35.8 ± 4.4	35.9 ± 4.6	277.1 ± 9.5	278.8 ± 10.4	28.3 ± 5.0	27.5 ± 5.4	NA	NA	3633 ± 519	3540 ± 471
Wang LF (2015) [12]	30.20 ± 2.69	29.51 ± 2.71	NA	NA	22.39 ± 3.24	21.21 ± 2.99	541	452	3342.52 ± 73.24	3343.64 ± 408.09
Aviram A (2016) [49]	34.1 ± 6.0	31.1 ± 5.2	35.4 ± 0.8	35.4 ± 0.8	NA	NA	52	660	2701 ± 532	2532 ± 431
Berglund SK (2016) [50]	33.7 ± 4.6	30.9 ± 4.2	39.2 ± 1.5	39.4 ± 1.2	27.7 ± 6.2	22.0 ± 1.7	41	73	3310 ± 4600	3250 ± 3900
Cosson E (2016) [51]	30.6 ± 5.8	29.6 ± 5.8	NA	NA	24.9 ± 4.8	24.6 ± 4.7	780	5708	NA	NA
Hilden K (2016) [52]	31.7 ± 5.2	29.9 ± 5.0	NA	NA	NA	NA	1798	373,778	3506 ± 586	3513 ± 536
Lai FY (2016) [53]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lu MC (2016) [54]	32.5	29.0	NA	NA	NA	NA	212	4627	NA	NA

Table 4 (continued)

First author (year)	Maternal age†		Completed weeks' gestation†		Pregestational BMI†		Nullipara, *n*		Birth weight†	
	GDM	Nondiabetic	GDM	Nondiabetic	GDM	Nondiabetic	GDM	Nondiabetic	GDM	Nondiabetic
	(32.0–32.9)	(28.9–29.1)								
Nguyen TH (2016) [55]	32.2 ± 5.1	31.1 ± 4.9	NA	NA	26.6 ± 5.7	23.9 ± 5.0	NA	NA	NA	NA
Peixoto AB (2016) [56]	27.6 ± 6.5	25.4 ± 6.3	38.2 ± 1.5	37.8 ± 2.8	NA	NA	NA	NA	3152 ± 546	2860 ± 681
Tward C (2016) [57]	34.8 ± 5.3	34.2 ± 5.2	34.4 ± 2.7	35.4 ± 2.4	NA	NA	56	636	2234 ± 650	2388 ± 557
Anand SS (2017) [58]	31.2 ± 4.0	29.7 ± 3.8	38.8 ± 1.6	39.3 ± 1.4	24.9 ± 4.6	23.2 ± 4.3	123	283	3267 ± 23	3181 ± 17
Beka Q (2017) [59]	32.1 ± 5.3	29.1 ± 5.4	NA	NA	NA	NA	4509	134,507	NA	NA
Billionnet C (2017) [60]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bogdanet D (2017) [61]	34 (31–37)	32 (28–35)	39 (38–40)	40 (39–41)	32 (28–37)	26 (23–29)	226	1097	3580 (3240–3930)	3570 (3240–3920)
Bricelj K (2017) [62]	31.4 ± 5.1	29.5 ± 5.1	NA	NA	NA	NA	187	4146	2769 ± 539	2636 ± 473
Egan AM (2017) [63]	32.0 ± 5.0	31.9 ± 5.4	39.8 ± 9.6	39.5 ± 3.0	33.4 ± 4.7	33.7 ± 4.2	NA	NA	3488 ± 657	3456 ± 524
Feng H (2017) [13]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jiang S (2017) [64]	30.5 (27–34)	30.0 (27–33)	NA	NA	25.78 (21.71–29.85)	23.44 (20.27–26.62)	NA	NA	NA	NA
Koivunen S (2017) [65]	31.02 ± 5.45	29.39 ± 5.27	39.62 ± 1.66	39.87 ± 1.75	28.2 ± 6.11	23.8 ± 4.36	2634	22,290	3595 ± 561	3505 ± 539
Lauring JR (2017) [66]	31.0 (27.0–32.5)	28.0 (24.0–32.0)	38.9 (37.1–39.4)	39.3 (38.6–40.23)	29.9 (25.3–35.4)	25.0 (22.0–29.0)	18	1151	3362.5 (2947.5–3620.0)	3365.0 (3035.0–3690.0)
Liao S (2017) [67]	31.4 ± 4.8	31.3 ± 4.2	38.2 ± 2.1	39.6 ± 1.1	27.2 ± 4.8	26.2 ± 4.2	NA	NA	3449 ± 534	3460 ± 450
Lobmaier SM (2017) [68]	33 ± 5.4	33 ± 4.2	38.9 ± 1.3	39.9 ± 1.1	26.6 ± 8.2	23.1 ± 4.3	49	38	3340 ± 499	3473 ± 415
Metcalfe A (2017) [69]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mortier I (2017) [70]	34 (20–44)	28 (16–42)	39.3 ± 1.6	39.5 ± 1.4	NA	NA	18	149	3635.4 ± 588.0	3344.7 ± 520.3
Rosen H (2017) [71]	32.7 ± 4.8	30.4 ± 5.0	38.7 ± 1.0	39.3 ± 1.2	NA	NA	720	13,667	3221 ± 298	3227 ± 304
Vally F (2017) [72]	NA	NA	NA	NA	NA	NA	115	115	NA	NA
Wahabi H (2017) [73]	31.5 ± 5.9	29.5 ± 5.7	NA	NA	NA	NA	378	1655	NA	NA
Yan Y (2017) [74]	29.12 ± 7.15	28.71 ± 7.21	38.20 ± 0.11	38.18 ± 0.17	21.1 ± 6.3	20.6 ± 5.1	NA	NA	NA	NA
Ours	28.98 ± 4.50	27.08 ± 4.10	38.85 ± 1.67	39.02 ± 1.80	NA	NA	1195	9982	3476.34 ± 536.63	3321.82 ± 489.79

GDM, gestational diabetes mellitus; *NA*, not available

† Mean ± SD, median (range) or mean/median (interquartile range)

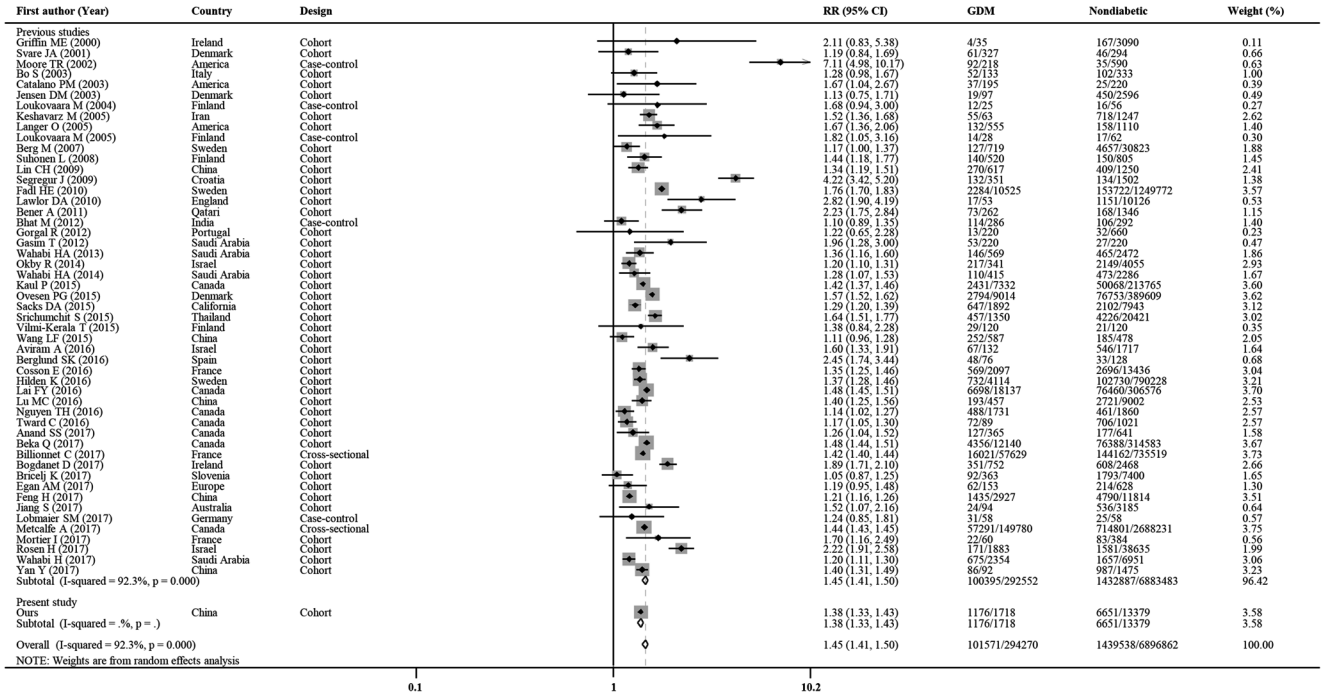

Fig. 2 Forest plot of RR and 95% CIs of studies of cesarean section. RR, relative risk; CI, confidence interval; GDM, gestational diabetes mellitus

[81–84]. GDM is a well-established risk factor for high birth weight with an incremental range from 15 to 62.5% [85–91], exceeding the risk of the general obstetric population [30]. The definition of macrosomia in this cohort is based on birth weight ≥ 4000. The results also show GDM is an important independent risk factor for offspring with high birth weight. After adjustment for gestational age and gestational hypertension, GDM could predict the increased risk for macrosomia and LGA. More importantly, our study shows that GDM plays a significantly beneficial effect on LBW and SGA of the infant. The subgroup meta-analysis excluding our cohort shows that GDM has no statistical association with LBW and SGA, but the trend of protective factors of GDM still exists. This may be due to the variety of population combined with diverse approaches to screening and diagnosis of GDM.

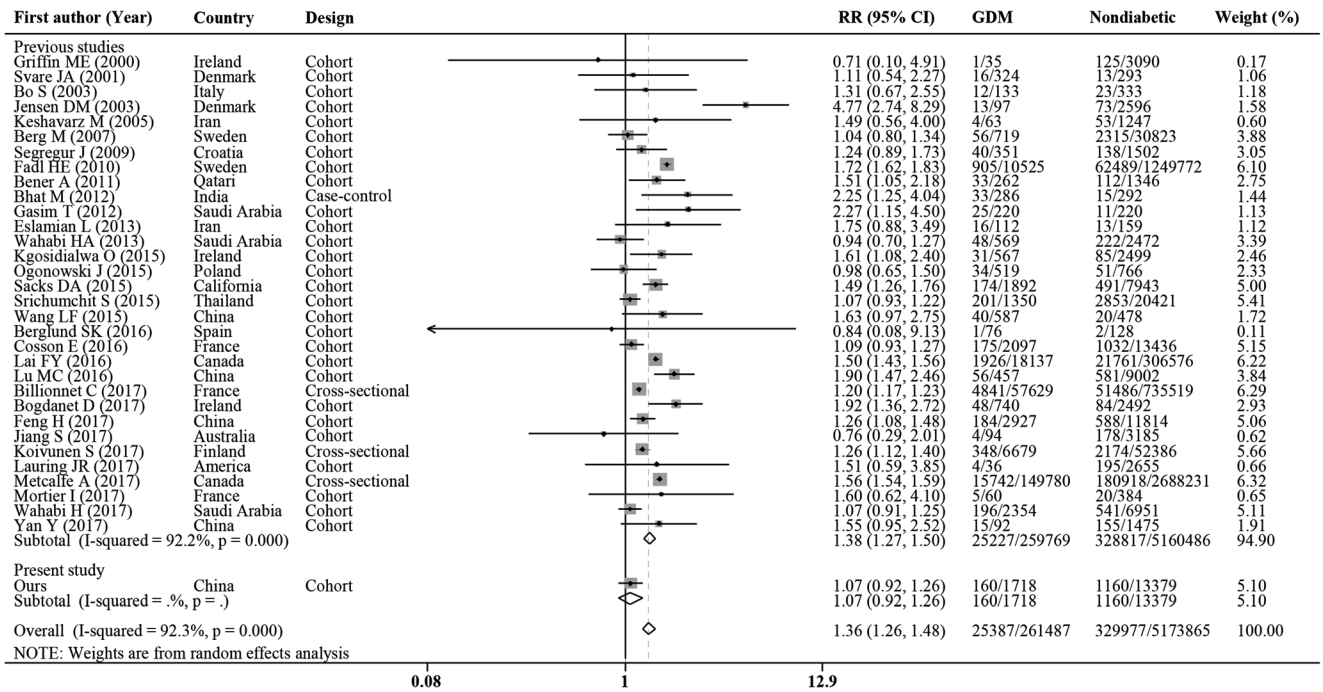

Fig. 3 Forest plot of RR and 95% CIs of studies of preterm birth. RR, relative risk; CI, confidence interval; GDM, gestational diabetes mellitus

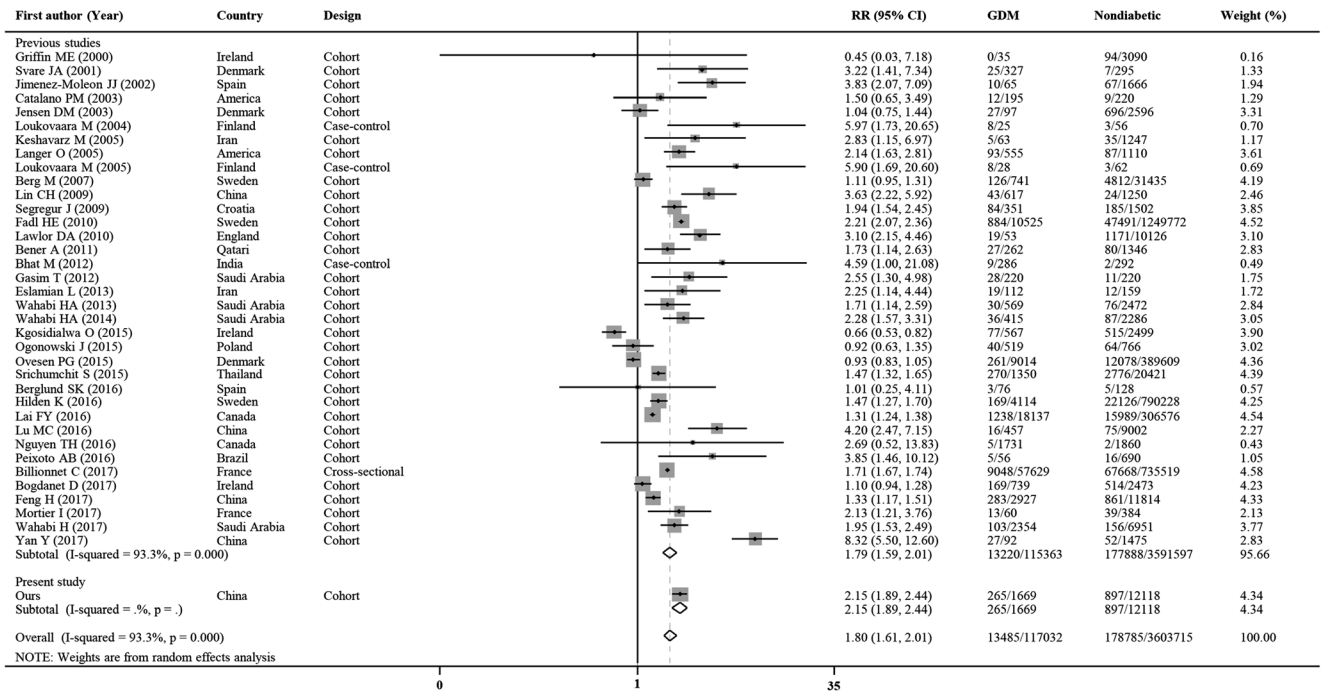

Fig. 4 Forest plot of RR and 95% CIs of studies of macrosomia. RR, relative risk; CI, confidence interval; GDM, gestational diabetes mellitus

Several characteristics of the study should be acknowledged. The relatively larger sample size makes it possible to adjust several potential confounders and minimize the possibility of selection bias regarding the exposure (GDM) and the reference group. Additionally, the accumulated evidence and the expanded sample size providing a more accurate and reliable evaluation of the effect make the statistical power relatively strong. The authenticity of cohort study, together with the nature of, meta-analysis, would help to obtain the pooled results and develop prospective insights based on evidence-based medicine.

Our study also has some limitations need to be addressed. Firstly, with regard to the study design of retrospective cohort in our cohort study, the origin of recollection in pregnant

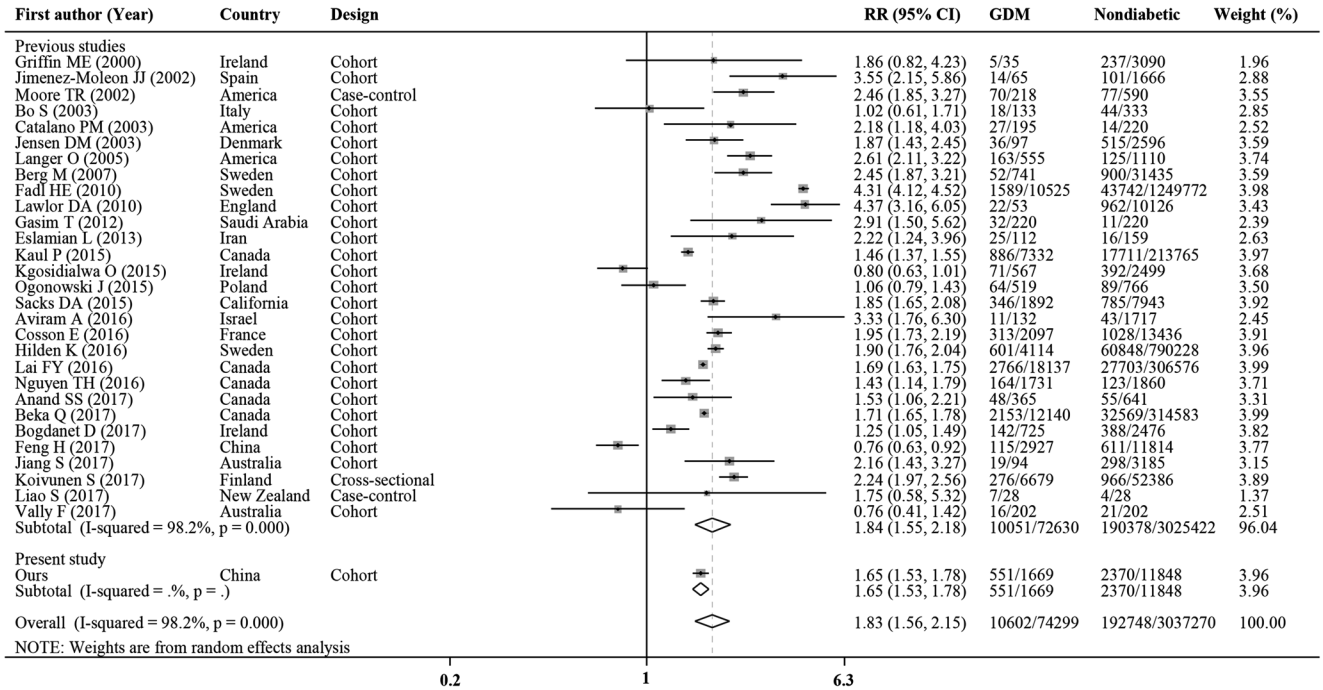

Fig. 5 Forest plot of RR and 95% CIs of studies of LGA. LGA, large for gestational age; RR, relative risk; CI, confidence interval; GDM, gestational diabetes mellitus

period is inclined to access incomplete and inaccurate information for those participants. Secondly, the incidence of neonatal complications is relatively low. So the statistical power of secondary outcomes is still limited.

Conclusion

In conclusion, our study has recognized some important maternal and neonatal outcomes for GDM patients with consideration of potential covariates, highlighting the clinical importance of GDM. Our study would be conductive to provide a comprehensive profile of GDM adverse outcomes and summarize the evidence of perinatal outcomes. More studies should attempt to focus on personal prevention and therapy strategies to mitigate the increasingly high prevalence.

Authors' contributions Concept and design: YS, YLJ, JZ, JC, LYJ.
Statistical analysis: YS, YLJ, JZ, LYJ.
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Methodology: YLJ, JZ, XYC, HYH, CQS.
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Compliance with ethical standards

Ethics approval and consent to participate All participants were provided written informed consent. The study protocol was performed in accordance with the Declaration of Helsinki and approved by the Ethical Review Committee of Nantong University; The Affiliated Hospital of Nantong University (AHNU) and the Nantong Maternal and Child Health Hospital (NMCHH).

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Gestational diabetes mellitus, its associated factors, and the pregnancy outcomes among pregnant women attending tertiary care hospitals of Bhubaneswar, India

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Abstract

Background Worldwide, there is an increasing trend in incidence of gestational diabetes mellitus (GDM) which may result in serious complications for the mother and the fetus. The study aimed to determine the prevalence of GDM and its associated factors among pregnant women attending tertiary care hospitals in Bhubaneswar and assessed the maternal and neonatal complications associated with GDM.

Methods This observational study was undertaken during the year 2015–2016 involving 218 eligible pregnant women with estimated gestational age between 24th and 32nd weeks. Venous blood samples were collected for estimation of plasma glucose. According to Diabetes in Pregnancy Study Group India (DIPSI) criteria, a woman was considered to have GDM if the 2-h plasma glucose value was ≥ 140 mg/dl.

Results The prevalence of gestational diabetes among pregnant women was estimated at 13.8%. Women with increasing age {AOR (adjusted odds ratio): 1.44, 95% CI: 1.23–1.67}, women with higher body mass index (AOR: 3.85, 95% CI: 1.31–11.11), women who had diabetic mother (AOR: 6.27, 95% CI: 1.95–20.15), and women who had gained more weight during pregnancy (AOR: 1.30, 95% CI: 1.09–1.56) were at higher risk of developing GDM. The analysis showed that women with GDM were significantly at higher risk of having polyhydramnios (AOR: 5.27, 95% CI: 1.34–20.78), postpartum hemorrhage (AOR: 9.39, 95% CI: 1.09–80.41), and preterm delivery (AOR: 8.52, 95% CI: 1.47–49.21).

Conclusion Early diagnosis and appropriate management of gestational diabetes among pregnant women may have far-reaching repercussions for maternal and child health.

Keywords Gestational diabetes · DIPSI criteria · Body mass index · Polyhydramnios · Postpartum hemorrhage · Preterm delivery

Introduction

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance with its inception during pregnancy [1] and leads to adverse maternal and neonatal outcomes [2, 3]. If diabetes in pregnancy is not adequately controlled in time, it results in higher incidence of congenital abnormalities, respiratory distress syndrome, neonatal hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia, polycythemia, and increased neonatal birth weight, thus increasing neonatal morbidity and mortality [4, 5]. In majority of cases, women with gestational diabetes do not show any symptom but may result in frequent urination, nausea, vomiting, tiredness, and bladder infection [6]. Further, poorly controlled glycemia during pregnancy may lead to various maternal complications such as abortion, polyhydramnios , preterm labor, preeclampsia, placenta previa, urinary tract infection, and puerperal sepsis [7]. Thus,

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early diagnosis of GDM is vital as it helps in taking remedial measures to lessen its negative impact on maternal and neonatal health.

During the last decade, the prevalence of GDM is increasing worldwide and more in developing countries including India. There is a large variation in the prevalence of GDM between different countries as it ranges between 2 and 40% [8–12], whereas in India, various studies have shown the prevalence of GDM in the range of 3 to 35% [13–17]. Different types of studies conducted in different parts of the world have identified various risk factors responsible for GDM which include advanced maternal age, overweight or obesity, history of abortion, preeclampsia, family history of diabetes, and high neonatal birth weight [1, 4, 9, 18].

To the best of our knowledge, very few studies have been conducted to examine the profile of GDM among pregnant women in the eastern region of India [19, 20]. The main purpose of this study was to determine the prevalence of GDM and associated factors among pregnant women attending tertiary care hospitals in Bhubaneswar and to assess the feto-maternal complications associated with GDM.

Methodology

Design and study population

This study was carried out in the outpatient departments (OPD) of obstetrics and gynecology of three tertiary care hospitals of Bhubaneswar City during the year 2015–2016. Geographically these three hospitals are located in the north, west, and east zones of the city and cater to the population of the entire city. Assuming prevalence of GDM as 16.2% [17] with 5% absolute precision at 95% level of confidence, a sample size of 209 was calculated. All the pregnant women with estimated gestational age between 24th and 32nd weeks attending OPDs of these hospitals for antenatal checkup were included in the study. Exclusion criteria included pre-existing diabetes; unwillingness to deliver at the study hospitals; multiple pregnancies; history of chronic diseases such as cardiovascular, respiratory, renal, hepatic disorder, etc.; and drugs that might affect pregnancy outcomes. Also, women with history of smoking or alcohol consumption or any drug dependence were excluded from our study. Overall, 230 eligible pregnant women were approached for the study, and 218 (94.8%) agreed to participate. Almost equal numbers of participants from each of the three hospitals were recruited for the study. The study protocol was approved by the Institutional Ethics Committee of the authors' institution, and permission from appropriate authorities of all the institutes was sought before initiation of the study. All the procedures in the study were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all the study participants prior to involvement in the study.

Procedures

Sociodemographic data were obtained from all of the study participants using a pretested, semi-structured schedule that consisted age, education, occupation, socioeconomic status, and details on medical and obstetric history, such as parity, past history of abortion, family history of diabetes and hypertension, etc. All of the women were examined for the presence of anemia, and their weight, height, and blood pressures were recorded. Body mass index (BMI) was calculated according to pre-pregnancy weight reported by the participants. In addition, urine samples of all the participants were analyzed.

All the participants were given 75-g oral glucose load dissolved in 300 ml of water irrespective of the time of last meal, and the venous blood samples were collected after 2 h. The plasma glucose was estimated by glucose-peroxidase (GOD-POD) method. According to Diabetes in Pregnancy Study Group India (DIPSI) criteria, a woman was considered to have GDM if the 2-h plasma glucose value was ≥ 140 mg/dl [21]. For the women who had GDM, antenatal care was given weekly during the third trimester, and GDM was properly managed with diet, exercise, and insulin as needed at the respective hospitals, whereas non-GDM women were followed up by obstetricians every 2 weeks until delivery. For assessing maternal and neonatal health consequences, both groups were followed for a week after delivery.

Pregnancy outcomes

Maternal outcomes after delivery were recorded in both GDM and non-GDM groups which included polyhydramnios, postpartum hemorrhage, premature delivery, and premature rupture of membranes. Neonatal outcomes included stillbirth, hyperbilirubinemia, and congenital malformation. Weight of all the neonates at the time of birth was recorded. Polyhydramnios was diagnosed on the basis of clinical suspicion and confirmed by findings on ultrasonography. Postpartum hemorrhage referred to blood loss in excess of 500 ml, from various sites like the uterus, cervix, vagina, and perineum after delivery of the baby. Preterm delivery was defined as delivery before 37 weeks of gestation. Stillbirth was defined as delivery of a dead baby at or after 22 weeks of gestation. Premature rupture of the membranes referred to rupture of the membranes before beginning of the labor and 37 weeks of pregnancy. Hyperbilirubinemia was defined as increase in total serum bilirubin level of > 12 mg/dl or neonatal treatment with phototherapy.

Table 1 Demographic and reproductive characteristics of study population ($n = 218$)

Characteristics	N (%)	GDM N (%)	Unadjusted OR (95% CI)	*p* value
Age (Mean ± SD)	25.78 ± 3.99	31.30 ± 4.17	1.39 (1.23–1.57)	0.00
Body mass index (kg/m^2)				
≥ 25	61 (32.4)	21 (70.0)	4.76 (2.08–11.11)	0.00
< 25	127 (67.6)	9 (30.0)	1	–
Education				
Up to 10th	97 (51.6)	13 (43.3)	0.72 (0.33–1.56)	0.40
10th and above	91 (48.4)	17 (56.7)	1	–
Occupation				
Housewife	166 (88.3)	25 (83.3)	0.66 (0.23–1.90)	0.45
Working woman	22 (11.7)	5 (16.7)	1	–
Socioeconomic status				
Upper	40 (21.3)	6 (20.0)	1.95 (0.36–10.41)	0.43
Upper middle	35 (18.6)	9 (30.0)	3.34 (0.67–16.79)	0.14
Lower middle	87 (46.3)	13 (43.3)	1.94 (0.41–9.17)	0.40
Upper lower	26 (13.8)	2 (6.7)	1	–
Parity				
Nulliparous	105 (55.9)	10 (33.3)	0.39 (0.17–0.89)	0.02
Multiparous	83 (44.1)	20 (66.7)	1	–
History of abortion				
Present	34 (18.1)	10 (33.3)	2.26 (0.97–5.27)	0.06
Absent	154 (81.9)	20 (66.7)	1	–
History of diabetes in mother				
Present	62 (33.0)	21 (70.0)	4.74 (2.05–10.96)	0.00
Absent	126 (67.0)	9 (30.0)	1	–
History of diabetes in father				
Present	71 (37.8)	19 (63.3)	2.84 (1.28–6.33)	0.01
Absent	117 (62.2)	11 (36.7)	1	–
History of hypertension in mother				
Present	51 (27.1)	13 (43.3)	2.05 (0.93–4.53)	0.07
Absent	137 (72.9)	17 (56.7)	1	–
History of hypertension in father				
Present	63 (33.5)	11 (36.7)	1.15 (0.51–2.56)	0.73
Absent	125 (66.5)	19 (63.3)	1	–
Anemia				
Present	41 (21.8)	8 (26.7)	1.29 (0.54–3.12)	0.55
Absent	147 (78.2)	22 (73.3)	1	–
Weight gain in Pregnancy (Mean ± SD)	8.77 ± 2.61	9.67 ± 3.78	1.11 (0.98–1.26)	0.11

Note: GDM, gestational diabetes mellitus; OR, odds ratio; SD, standard deviation; CI, confidence interval

Statistics

Data were analyzed using SPSS version 21.0 software. Univariable and multivariable logistic regression analyses were used to assess the relationships between variables and to adjust for potential confounders. All variables found to have $p < 0.2$ in univariable analyses were entered in the multivariable regression models. All p values were two tailed, and $p < 0.05$ was considered as significant. In the multivariable models, independent variables having significant associations with the dependent variable were examined for the presence of any interactions. Models chi square statistic and Hosmer-Lemeshow statistic were checked to assess whether the model adequately fits the data.

Table 2 Multivariable regression analysis showing factors associated with GDM among study population ($n = 218$)

GDM		
Characteristics	Adjusted OR (95% CI)	*p* value
Age (year)	1.43 (1.23–1.66)	0.000
Body mass index (kg/m^2)		
≥ 25	3.72 (1.28–10.81)	0.016
< 25	1	–
Parity		
Nulliparous	0.93 (0.26–3.28)	0.906
Multiparous	1	–
History of abortion		
Present	0.53 (0.13–2.24)	0.393
Absent	1	–
History of diabetes in mother		
Present	6.32 (2.00–19.99)	0.002
Absent	1	–
History of diabetes in father		
Present	1.25 (0.40–3.87)	0.704
Absent	1	–
History of hypertension in mother		
Present	1.29 (0.35–4.71)	0.703
Absent	1	–
Weight gain in pregnancy	1.27 (1.05–1.54)	0.012

Note: GDM, gestational diabetes mellitus; OR, odds ratio; SD, standard deviation; CI, confidence interval; $p < 0.05$ (statistically significant); model $\chi^2 = 70.856$, $p < 0.001$, and Hosmer and Lemeshow $p = 0.286$ indicates that the model adequately fits the data. Nagelkerke's $R^2 = 0.503$. The classification table reports that overall expected model performance is 92.2% that is 92.2% of the cases and can be expected to be classified correctly by the model

Table 3 Pregnancy outcomes of GDM among study population ($n = 218$)

Outcomes	Non-GDM *N* (%)	GDM *N* (%)	Unadjusted OR (95% CI)	*p* value
Polyhydramnios				
Yes	25 (13.3)	11 (36.7)	3.77 (1.61–8.86)	0.002
No	163 (86.7)	19 (63.3)	1	
Postpartum hemorrhage				
Yes	8 (4.3)	3 (10.0)	2.50 (0.62–10.01)	0.195
No	180 (95.7)	27 (90.0)	1	
Gestational hypertension				
Yes	5 (2.7)	4 (13.3)	5.63 (1.42–22.32)	0.014
No	183 (97.3)	26 (86.7)	1	
Preterm birth (< 37 weeks)				
Yes	7 (3.7)	5 (16.7)	5.17 (1.52–17.54)	0.008
No	181 (96.3)	25 (83.3)	1	
Membranes ruptured (< 37 weeks)				
Yes	2 (1.1)	1 (3.3)	3.21 (0.28–36.5)	0.348
No	186 (98.9)	29 (96.7)	1	
Preeclampsia				
Yes	3 (1.6)	1 (3.3)	2.13 (0.21–21.14)	0.520
No	185 (98.4)	29 (96.7)	1	
Stillbirth				
Yes	8 (4.3)	2 (6.7)	1.61 (0.32–7.96)	0.561
No	180 (95.7)	28 (93.3)	1	
Jaundice				
Yes	20 (10.6)	5 (16.7)	1.68 (0.58–4.88)	0.340
No	168 (89.4)	25 (83.3)	1	
Birth weight (kg) (Mean ± SD)	2.71 ± 0.31	2.88 ± 0.33	5.08 (1.52–17.05)	0.008

Note: GDM, gestational diabetes mellitus; OR, odds ratio; SD, standard deviation; CI, confidence interval

Table 4 Multivariable regression analysis showing outcomes associated with GDM among study population ($n = 218$)

GDM		
Outcomes	Adjusted OR (95% CI)	p value
Polyhydramnios		
Yes	5.27 (1.34–20.78)	0.018
No	1	
Postpartum hemorrhage		
Yes	9.39 (1.09–80.41)	0.041
No	1	
Gestational hypertension		
Yes	3.31 (0.42–26.15)	0.257
No	1	
Preterm birth (< 37 weeks)		
Yes	8.52 (1.47–49.21)	0.017
No	1	
Birth weight (kg)	2.64 (0.44–15.73)	0.286
Age (year)	1.42 (1.22–1.64)	0.000
BMI (kg/m^2)	4.06 (1.14–14.46)	0.031
History of diabetes in mother		
Present	6.84 (1.94–24.15)	0.003
Absent	1	
Weight gain in pregnancy	1.18 (0.97–1.44)	0.094

Note: GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; $p < 0.05$ (statistically significant). Model $\chi^2 = 84.463$, $p < 0.001$, and Hosmer and Lemeshow $p = 0.970$ indicates that the model fits the data. Nagelkerke's $R^2 = 0.611$. The classification table reports that overall expected model performance is 92.8% that is 92.8% of the cases and can be expected to be classified correctly by the model

Results

Out of 235 eligible pregnant women approached for the study, 218 (92.7%) agreed to participate. The mean age of the study participants was 26.5 ± 4.4 years (range 18–38 years). The mean weight and BMI before pregnancy were 55.5 ± 9.1 kg and 24.0 ± 3.7 kg/m^2, respectively. In our study, the prevalence of GDM among 218 women of gestational age between 24 and 32 weeks was 13.8% based on DIPSI criteria. The mean 2-h plasma glucose values of women with GDM was 167.23 ± 24.82 mg/dl compared to 98.22 ± 13.96 mg/dl in normal women.

Table 1 shows the demographic and reproductive characteristics of study participants. Univariable analyses revealed that GDM was significantly more frequent among older women (OR: 1.39, 95% CI: 1.23–1.57), women who had BMI ≥ 25 kg/m^2(OR: 4.76, 95% CI: 2.08–11.11), women who were multiparous (OR: 2.56, 95% CI: 1.12–5.88), and women who had diabetic mother (OR: 4.74, 95% CI: 2.05–10.96) and diabetic father (OR: 2.84, 95% CI: 1.28–6.33). Also, women who had gained more weight during pregnancy were more likely to have GDM (OR: 1.11, 95% CI: 0.98–1.26). All the variables with $p < 0.2$ in univariable analyses were simultaneously entered in the multivariable regression model and adjusted for each other (Table 2). After adjustment of the confounders, multivariable analysis finally indicated that women with increasing age (AOR: 1.43, 95% CI: 1.23–1.66) and increasing BMI (AOR: 3.72, 95% CI: 1.28–10.81), women who had diabetic mother (AOR: 6.32, 95% CI: 2.0–19.99), and women who had gained more weight during pregnancy (AOR: 1.27, 95% CI: 1.05–1.54) were at higher risk of having GDM. There were no differences between the two groups in parity, history of abortion, history of diabetes in participant's father, and history of hypertension in participant's mother.

Table 3 shows the possible pregnancy outcomes of GDM. Univariable analyses suggested that women with GDM were at increased risk of having polyhydramnios (OR: 3.77, 95% CI: 1.61–8.86), gestational hypertension (OR: 5.63, 95% CI: 1.42–22.32), and preterm delivery (OR: 5.17, 95% CI: 1.52–17.54). In addition, neonates born to mothers with GDM were more likely to have higher birth weight (OR: 5.08, 95% CI: 1.52–17.05). All the outcome variables with $p < 0.2$ in univariable analyses as well as variables significantly associated with GDM such as age, BMI, history of diabetes, and weight gain in pregnancy were simultaneously entered in the multivariable model and adjusted for each other (Table 4). After adjustment of potential confounders, multivariable analysis revealed that women with GDM were significantly at higher risk of having polyhydramnios (AOR: 5.27, 95% CI: 1.34–20.78), postpartum hemorrhage (AOR: 9.39, 95% CI: 1.09–80.41), and preterm delivery (AOR: 8.52, 95% CI: 1.47–49.21).

Discussion

In the present study, we used DIPSI criteria, a modified WHO criterion to diagnose GDM which was designed as per Indian standards. It is a simple, convenient, economical, and single-step procedure which can be used as both diagnostic and screening test [20, 22] although few studies have reported about the low sensitivity of the DIPSI criteria [23–27]. To estimate the prevalence of GDM, studies across the world have adopted different screening and diagnostic criteria such as World Health Organization (WHO) 1999 criteria [14, 28], American Diabetes Association (ADA) criteria [9, 16, 19, 29, 30], International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [11, 14, 28], and National Diabetes Data Group (NDDG) criteria [31]. According to WHO 1999 criteria, diagnosis of GDM is made when fasting plasma glucose (FPG) level is ≥ 126 mg/dl (7.0 mmol/l) or 2-h plasma glucose (PG) level after 75-g oral glucose tolerance test (OGTT) is ≥ 140 mg/dl (7.8 mmol/l). As per ADA criteria, GDM is diagnosed when at least two of the four values, i.e., FPG ≥ 95 mg/dl (5.3 mmol/l), 1-h PG after 75 g OGTT ≥

180 mg/dl (10.0 mmol/l), 2-h PG after 75 g OGTT ≥ 155 mg/dl (8.6 mmol/l), and 3-h PG after OGTT ≥ 140 mg/dl (7.8 mmol/l), are met. IADPSG criteria defined GDM by FPG ≥ 92 mg/dl (5.1 mmol/l) or 1-h PG after 75 g OGTT ≥ 180 mg/dl (10 mmol/l) or 2-h PG after 75-g OGTT ≥ 153 mg/dl (8.5 mmol/l). According to NDDG criteria, GDM is defined if at least two or more readings are equaled or exceeded the levels of FPG 105 mg/dl (5.8 mmol/l), 1-h PG after 100-g OGTT 190 mg/dl (10.6 mmol/l), 2-h PG after 100-g OGTT 165 mg/dl (9.2 mmol/l), and 3-h PG after 100-g OGTT 145 mg/dl (8.1 mmol/l).

GDM comprised of 13.8% of the women screened in our study. In studies conducted in various cities of India during the last decade, the prevalence of GDM was 7.1% in Haryana [16], 18.5% in Tamilnadu [28], 9.7% in Uttarpradesh [32], 6.9% in Jammu [33], and 6.6% in Rajastan [15]. Melchior et al. reported a prevalence of GDM as 13.2% in a population-based survey conducted in Germany [10]. In another study, the prevalence of GDM in Turkish pregnant women was found to be 4.3% [9], whereas Alfadhli et al. in their study showed higher prevalence of GDM (39.4%) in pregnant Saudi women [4]. The variation in prevalence rates might be due to difference in diagnostic criteria and methods of testing used in different studies and geographic and ethnic variations in the study population.

In our study, it was observed that GDM was significantly associated with increasing age, higher BMI, history of diabetes in mother, and higher weight gain during pregnancy. The odds of developing GDM were increasing 1.43 times with 1 year increase in age. Similar result has been reported in previous literature [4, 14, 18, 34]. We also found that GDM was significantly higher in women with higher pre-pregnancy BMI. Women with BMI ≥ 25 kg/m^2 were 3.85 times more likely to have GDM than women with BMI < 25 kg/m^2. Rajput et al. reported an odds ratio of 4.6 for women with BMI > 25 kg/m^2 [16]. Higher prevalence of GDM in women with higher BMI has also been observed in earlier studies as well [4, 9, 35, 36].

In the present study, it was observed that women who had diabetic mothers were 6.27 times odds of developing GDM compared to those having non-diabetic mothers. However, GDM in women was not significantly associated with the presence of paternal diabetes. It has been widely reported that presence of family history of diabetes mellitus is associated with higher chances of developing GDM [4, 9, 16, 34, 37]. Furthermore, we observed that women with GDM had a significantly higher gain in weight compared to women without GDM. Various studies have shown significant association between excessive weight gain in pregnancy and GDM [9, 16, 38].

Our study supports previous reports that women with GDM have significantly higher proportion of obstetric complications including polyhydramnios, postpartum hemorrhage, and preterm delivery. In this study, women with GDM had 5.27 odds of having polyhydramnios as compared to women without GDM. This is in agreement with results of other literatures [31, 39, 40]. In the present study, it was found that postpartum hemorrhage was more likely to be present in the GDM group (AOR: 9.39, $p < 0.05$). Postpartum hemorrhage has higher incidence in GDM patients which might be due to over distended uterus with large babies, prolonged duration of labor, cervical tears, and vaginal lacerations [41]. We also observed that gestational hypertension was more frequent in women with GDM (statistically insignificant). In contrast, various studies have reported significant association of gestational hypertension with GDM [18, 42, 43]. In the present study, the odds of preterm delivery increases 8.52 times among GDM group than their counterparts. This is supported by the results of earlier studies [18, 42–44]. Although statistically insignificant, the neonates born to GDM mothers were heavier than those born to non-GDM mothers. Previous studies have also reported that women with GDM give birth to heavier neonates as compared to women without GDM [4, 18, 37].

The study has a few limitations. First, as the study participants were limited to women attending three tertiary care hospitals of Bhubaneswar, thus the findings may not be generalized to pregnant women visiting all types of health centers. Another limitation is that the causal association of various risk factors with GDM cannot be established as data were collected at one point in time (cross-sectional in nature). In addition, glycemic parameters and treatment modalities were not considered for the assessment of fetal outcome which might have affected the result of our study. However, the present study provides a clear insight regarding obstetric complications of GDM as the study participants were followed up for a certain period (prospective in nature), and thus the temporal associations between feto-maternal complications and GDM could be explored.

Conclusion

The GDM prevalence obtained in this study is 13.8% which is in the range of current international prevalence estimates. This commonly occurring medical disorder in pregnancy should be timely diagnosed, monitored, and appropriately managed in order to prevent feto-maternal complications. We also recommend that promoting healthy lifestyle interventions and increasing awareness of GDM risk factors can prevent GDM in pregnant women and improve their quality of life.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Research involving human participants All the procedures performed in the present study involving human participants were in accordance with the ethical standards of the Institutional Ethics Committee of Kalinga Institute of Medical Sciences (Reference number: KIMS/ETHICS/522/2014) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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ORIGINAL ARTICLE

Diagnostic efficiency of diabetes in pregnancy study group of India versus World Health Organization 2013 criteria

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Abstract

Background Diagnostic criterion for abnormal glucose tolerance (AGT) in pregnancy is still under debate. This study aims to see the diagnostic efficiency of Diabetes in Pregnancy Study Group of India (DIPSI) criterion in context to World Health Organization (WHO) 2013 criterion for detection of AGT in pregnancy.

Methods Pregnant mothers ($n = 231$; age, 26.07 ± 5.21 years; body mass index (BMI), 25.00 ± 4.09 kg/m^2; mean ± SD) were screened for AGT including gestational diabetes mellitus (GDM) and diabetes in pregnancy (DIP) from July 2016 to July 2017 in the "GDM Clinic" of BSMMU following WHO 2013 and DIPSI protocol with an interval of 3–5 days in between. Out of 231 mothers, 204 completed both procedures. Diagnostic efficiency of DIPSI criterion was assessed in the light of WHO 2013 criterion.

Results Out of 204 mothers, 61 (29.9%) had AGT (GDM = 55, DIP = 6) according to WHO 2013 criterion whereas only 36 (17.6%) had AGT (GDM = 33, DIP = 3) by DIPSI criterion. Among participants, age (25.50 ± 5.11 vs. 27.39 ± 5.28, $p = 0.018$) and BMI (24.50 ± 3.92 vs. 26.31 ± 4.41, $p = 0.003$) were significantly higher in AGT group than the group with normal glucose tolerance (NGT).Holding WHO 2013 criterion as gold standard, specificity of DIPSI criterion was very high (93.70%), but sensitivity was relatively low (44.26%). There was a fair agreement between the two criteria (kappa = 0.43; $p < 0.001$). The 2-h glucose values in same subjects were found to be lower when tested for DIPSI criterion protocol in comparison to that WHO 2013 protocol.

Conclusion DIPSI criterion seems to be less sensitive in context to WHO 2013 criterion for detection of AGT in pregnancy.

Keywords GDM · DIP · AGT · WHO 2013 · DIPSI criteria

Introduction

Abnormal glucose tolerance (AGT) in pregnancy which includes gestational diabetes mellitus (GDM) and diabetes in pregnancy (DIP) is associated with both short-term and long-term fetal and maternal adverse outcomes [1, 2].The World Health Organization (WHO) at 2013 differentiated AGT into GDM and DIP based on status of abnormal glycemia irrespective of trimester [3]. The worldwide incidence of GDM is increasing in parallel with the pandemic obesity and type 2 diabetes mellitus (T2DM) [4–6]. It was estimated by International Diabetes Federation (IDF) that 20.9 million (16.2%) of live births to women in 2015 had some form of hyperglycemia in pregnancy and its highest prevalence is observed among Southeast Asia region (24.2%) [7]. Recent studies in a tertiary level hospital of Bangladesh revealed higher prevalence of GDM, 36.6% according to WHO 1999 criterion [8] and 35.5% according to WHO 2013 criterion [9]. Moreover, our ethnicity is regarded as high-risk group [10]. So universal screening of AGT in pregnancy with timely intervention to achieve euglycemia needs to be considered in community where prevalence of GDM is high like Bangladesh. Different diagnostic criteria are used in different countries even within the same country. An ideal diagnostic criterion for diagnosis of GDM is still a question of debate. Three sample oral glucose tolerance test (OGTT)-based diagnostic criteria is more scientific and based on pregnancy outcome proven by the hyperglycemia and adverse pregnancy outcome (HAPO) study but may be difficult to apply for mass screening

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Table 1 WHO 2013 and DIPSI criteria for diagnosis of abnormal glucose tolerance in pregnancy irrespective of gestational weeks

Criteria	GDM	DIP
WHO 2013		
Diagnostic cutoff on OGTT		
FPG (mmol/L)	≥ 5.1	≥ 7.0
1-h PG (mmol/L)	≥ 10.0	
2-h PG (mmol/L)	≥ 8.5	≥ 11.1
DIPSI		
After 75 g glucose challenge		
2 h PG (mmol/L)	≥ 7.8–11.0	≥ 11.1

WHO World Health Organization, *GDM* gestational diabetes mellitus, *DIP* diabetes in pregnancy, *FPG* fasting plasma glucose, *PG* plasma glucose, *DIPSI* diabetes in pregnancy study group India, *OGTT* oral glucose tolerance test

specially at community level due to some barrier related to it [11]. A simple, cost-effective, and easy approach was proposed by some researchers in India, known as diabetes in pregnancy study group of India (DIPSI) to apply it at community level for mass screening [12]. Though DIPSI diagnostic criterion is easy to carry out to screen mass population for its simplicity, some study reports are not well convinced with this criterion [13–18]. Previously Panthi et al. observed some discrepancies between DIPSI criterion and WHO 2013 criterion in Bangladeshi population [9]. But the study did not perform a non-fasting glucose challenge test on a separate day, rather only evaluated DIPSI cutoffs interposed over formal 3-sample OGTT. The present study was carried out to see the efficiency of DIPSI criterion for detection of AGT during pregnancy holding WHO 2013 criterion as gold standard.

Materials and methods

Study subjects

This study was intended to screen 231 pregnant subjects for AGT (age, 26.07 ± 5.21 years; body mass index (BMI) 25.00 ± 4.09 kg/m^2; mean ± SD) by 03 samples OGTT according to WHO 2013 criterion followed by single-sample DIPSI criterion with an interval of 3–5 days. Finally, 204 subjects completed both the tests. They were recruited from antenatal clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, irrespective of trimester and presence of risk factors of GDM. Any women with prior history of GDM or DM were excluded from the study.

Study design

It was a cross-sectional study carried out at the "GDM clinic" of BSMMU from July 2016 to July 2017 after approval by the Institutional Review Board (IRB). Three sample OGTT was done according to WHO protocol while single sample glucose challenge test according to DIPSI protocol irrespective of prandial state was done in the morning at around 10 am to

Table 2 Characteristics of study subjects ($n = 231$)

Characters/variables	Frequency	Percentage	mean ± SD
Age (mean ± SD, year)	–	–	26.07 ± 5.21
BMI (mean ± SD, kg/m^2)	–	–	25.00 ± 4.09
Systolic BP (mean ± SD, mmHg)	–	–	109.46 ± 11.92
Diastolic BP (mean ± SD, mmHg)	–	–	69.59 ± 8.98
Family history of DM	86	37.4%	–
History of abortion	63	27.3%	–
Gravida			
Primigravida	101	43.7%	–
Multigravida	130	56.3%	–
Trimester at presentation			
1st Trimester	35	15.2%	–
2nd Trimester	96	41.5%	–
3rd Trimester	100	43.3%	–
Occupation			
Housewife	162	70.1%	–
Service holder	45	19.5%	–
Students	24	10.4%	–

(Percentages are over column total)

BMI body mass index, *SD* standard deviation

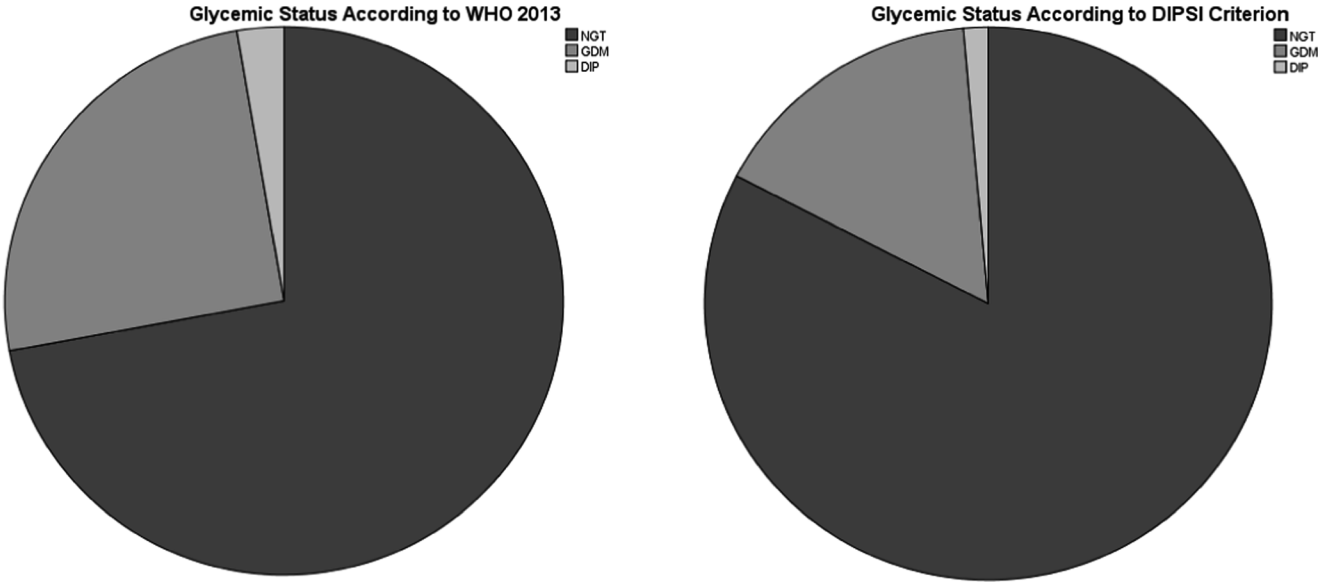

Fig. 1 Glycemic status comparison between WHO 2013 and DIPSI criteria. *WHO* World Health Organization, *DIPSI* diabetes in pregnancy study group India

12:30 pm. AGT was detected based on either WHO 2013 or DIPSI criterion (Table 1). Demographic and clinical variables including height, weight, BMI (kg/m^2), and blood pressure (mm Hg) were recorded in structured data collection sheet for analysis.

Analytic method

The samples were centrifuged after collection and transported to laboratory in pre-labeled test tubes. Plasma glucose was assayed by glucose oxidase method on the same day in automated analyzer [RA-50 analyzer (Dade Behring, Germany)]. Report was immediately collected and preserved.

Table 3 Agreement/disagreement of glycemic status according to DIPSI Criterion with WHO 2013 criterion ($n = 204$)

DIPSI	WHO 2013		Total
	AGT	NGT	
AGT	27 (44.3)	9 (6.3)	36 (82.4)
NGT	34 (55.7)	134 (93.7)	168 (17.6)
Total	61	143	204

Within parentheses are percentages over column total

By Kappa test, $\kappa = 0.430$; $p < 0.001$

AGT comprises both GDM and DIP, total 6 DIP were included in AGT

DIPSI diabetes in pregnancy study group India

WHO World Health Organization

AGT abnormal glucose tolerance

NGT normal glucose tolerance

GDM gestational diabetes mellitus

DIP diabetes in pregnancy

Statistical analysis

All data were processed in IBM SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY, USA) and expressed as frequencies or percentages as well as mean (± SD) as applicable. Agreement between two test methods for diagnosis of AGT was done by Kappa test. Sensitivity and specificity of DIPSI criterion was calculated holding WHO 2013 criterion as gold standard. p values ≤ 0.05 were considered significant statistically.

Results

The characteristics of study subjects are shown in Table 2. Frequency of AGT and NGT according to WHO 2013 and DIPSI criteria is depicted in Fig. 1. Comparison of glycemic status of the participants according to WHO 2013 and DIPSI criteria is shown in Table 3. It was observed that 9 subjects found NGT by WHO criterion were AGT by DIPSI criterion; on the other hand, 34 subjects with AGT by WHO 2013 criterion were found to be normal by DIPSI criterion. There was fair agreement between the two criteria ($\kappa = 0.430$; $p < 0.001$). As shown in Table 4, mean (± SD) age (years, 27.39 ± 5.28 vs. 25.50 ± 5.11; $p = 0.018$), BMI (kg/m^2, 26.31 ± 4.41 vs. 24.50 ± 3.92, $p = 0.003$), and diastolic BP (mmHg, 71.45 ± 9.16 vs. 68.72 ± 8.85, $p = 0.047$) were significantly higher among AGT group than NGT group. There was no difference in prevalence of AGT among different trimesters (22.9%, 29.3%, 28.4%, respectively, for 1st, 2nd, and 3rd trimester, $p = 0.759$). Diagnostic efficacy of DIPSI criterion is shown in Table 5. The 2-h plasma glucose values in same subjects were found to be lower when tested for DIPSI criterion in comparison to WHO 2013 (Table 6).

Table 4 Comparison of clinical variable between NGT and AGT (n = 222)

Characters/variables	NGT (n = 160)	AGT(n = 62)	p
Age (mean ± SD, year)	25.50 ± 5.11	27.39 ± 5.28	p = 0.018
BMI (mean ± SD, kg/m^2)	24.50 ± 3.92	26.31 ± 4.41	p = 0.003
Systolic BP (mean ± SD, mmHg)	108.78 ± 11.28	111.61 ± 13.17	p = 0.111
Diastolic BP (mean ± SD, mmHg)	68.72 ± 8.85	71.45 ± 9.16	p = 0.047
Family history of DM	51 (64.6%)	28 (34.4%)	p = 0.038
History of abortion	43 (71.7%)	17 (22.9)	p = 0.53
Gravida			
Primigravida	76 (76.8%)	23 (23.2%)	p = 0.162
Multigravida	84 (68.3%)	39 (31.7%)	
Trimester at presentation			
1st Trimester	27 (77.1%)	8 (22.9%)	p = 0.759
2nd Trimester	65 (76.7%)	27 (29.3%)	
3rd Trimester	68 (71.6%)	27 (28.4%)	
Occupation			
Housewife	113 (72.4%)	43 (27.6%)	p = 0.15
Service holder	28 (63.6%)	16 (36.4%)	
Students	19 (86.4%)	3 (13.6%)	

(Within parenthesis are percentages over row total)

AGT and NGT diagnosed on the basis of WHO 2013 criterion

AGT abnormal glucose tolerance

AGT comprises both GDM and DIP, total 6 DIP were included in AGT

DIP diabetes in pregnancy

GDM gestational diabetes mellitus

NGT normal glucose tolerance

Discussion

In the present study, alarmingly high frequency (28%) of AGT was observed by WHO 2013 criterion which was relatively low (17.6%) by DIPSI criterion. High frequency of AGT was also observed by some other tertiary care hospital-based studies of Bangladesh in recent years [8, 9]. Specificity of DIPSI criterion was observed to be very high (93.70%), but sensitivity was relatively low (44.26%), which is very similar to other studies [13, 14].

In comparison to other diagnostic tests for GDM, DIPSI criterion is unique for its simplicity and feasibility. It considers the limitation of resources and the tendency of pregnant mothers to avoid a test on fasting state. Since DIPSI proposed the criterion, it is well acknowledged to be applicable at community level. But concerns remained whether it will miss the cases of GDM as no fasting or 1 h value is tested. As the DIPSI criterion uses same glucose load like WHO 2013 and is done in non-fasting state, amount and type of food ingested before the test may influence the test result. In our study, 2-h plasma glucose value after glucose challenge in non-fasting state was significantly lower in DIPSI criterion than that of the WHO criterion in fasting state among same subjects in two different days. This difference contributed to relatively low sensitivity of DIPSI criterion seen in present study. Low 2-h plasma glucose value in DIPSI criterion could be explained to some extent by the Staub-Traugott effect: a lower glycemic response to a glucose load that follows another glucose challenge [19]. Meal intake before glucose challenge test as may happen according to DIPSI criterion could affect plasma glucose after glucose load depending upon duration of pretest meal intake, which is predominant if taken within 2 h of the procedure [20]. Most of the subjects in the present study, who underwent glucose challenge test by DIPSI protocol, took prior meal within 1–4 h which could have influenced the 2-h plasma glucose value and also lower the sensitivity of DIPSI criterion. Further studies may evaluate the impact of prior intake of food types and timing on the glycemic response during glucose challenge test. It also seems crucial to know the pregnancy outcomes of the WHO 2013 criterion GDM cases missed by DIPSI criterion. The present study was not designed to answer this question.

Table 5 Diagnostic efficacy of DIPSI criterion

DIPSI criterion	Efficacy
Sensitivity	44.26%
Specificity	93.70%
Positive predictive value	75.00%
Negative predictive value	79.76%
Accuracy	78.92%
Positive likely hood ratio	70.25%
Negative likely hood ratio	53.48%

DIPSI diabetes in pregnancy study group India

There was no statistically significant difference of the frequency of AGT among mothers in different trimesters and gestational weeks before or after 24 weeks. This observation is consistent with previous studies by our group [8, 9]. Most of the international guidelines generally recommend testing for GDM at 24–

Table 6 Comparison of 2-h plasma glucose in mmol/L (mean ± SD) on glucose challenge by WHO 2013 and DIPSI Criteria

Subject group	WHO 2013	DIPSI	p*
NGT (n = 143)	6.34 ± 1.09	6.15 ± 1.03	0.073
GDM (n = 55)	8.53 ± 1.49	7.35 ± 1.63	< 0.001
DIP (n = 6)	12.30 ± 1.32	10.75 ± 4.47	0.384
All subjects (n = 204)	7.11 ± 1.80	6.61 ± 1.66	< 0.001

*By paired Student's t-test between WHO 2013 vs. DIPSI

WHO World Health Organization

DIPSI diabetes in pregnancy study group India

OGTT oral glucose tolerance test

GDM gestational diabetes mellitus

NGT normal glucose tolerance

Glycemic status as observed by WHO 2013

28 weeks of gestation. But this recommendation may not be applicable in community with high prevalence of T2DM and GDM like ours. Frequency of continuation of pre-gestational diabetes in first trimester is also high that mandates urgent screening for AGT at first antenatal booking to prevent maternal and fetal complications.

Although DIPSI criterion is cost-effective and easy to perform, its low sensitivity might make it less suitable for generalized use. DIPSI criterion in fasting state at morning or fasting at least 4 h or more as an alternative approach might be considered to see its influence on sensitivity before recommending it for generalized use.

Conclusions

When compared to WHO 2013 criterion for detection of AGT in pregnancy, DIPSI criterion seems to be less sensitive but well-specific. Different glycemic response to same glucose load in two diagnostic procedures warrants further attention.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board (IRB) of BSMMU. All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRB and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed written consent was obtained from each of the participants included in the study.

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ORIGINAL ARTICLE

Gender-specific siblings and women with maternal history of diabetes are at high risk of developing type2 diabetes-a family study from South India

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Abstract

Background Risk factors associated with diabetes (DM) are to be well studied, and this study was aimed to investigate the family transmission pattern of type 2 DM in South Indian population.

Methods A total of 3093 subjects were selected between June 2017 and May 2018. Details on family history of diabetes, treatment, and age at onset of DM were recorded. The subjects are divided into three groups based on family history risk categories maintained as registries. Group 1 (NPDR) ($n = 1414$) was with no parent diabetes, group 2 (OPDR) ($n = 1216$) with one parent diabetes, and group 3 (CPDR) ($n = 463$) was with both parents diabetes. The history of diabetes in siblings was recorded. Diagnosis of diabetes was confirmed based on the history of treatment and by OGTT.

Results In group 2, genderwise comparison showed higher transmission of diabetes from mothers than fathers. Women had more maternal history of diabetes than paternal history [58.1 vs 41.9%; $p < 0.001$]. In men, the number of brothers affected by diabetes was higher than sisters (78 vs 29%; $p < 0.001$) whereas in women, the number of sisters affected was higher than brothers (70.3 vs 45.7%; $p < 0.001$). In groups 2 and 3, mean age at onset of diabetes in the subjects was one decade earlier than the mean age at onset of diabetes in parents.

Conclusion Gender-specific siblings and women with maternal history of diabetes are at high risk of developing type 2 DM. Men had higher percentage of brothers affected whereas women had higher percentage of sisters affected by diabetes. The mean age at onset of diabetes in subjects was a decade earlier than mean age at onset of diabetes in their parents.

Keywords Familial aggregation · Type 2 diabetes · Maternal history · Risk of diabetes · South India

Introduction

Diabetes mellitus (DM) has become a global health issue which occupies the epidemic proportion in developing countries of the world. In view of rising prevalence of diabetes and its economic consequences, prevention of diabetes among people at high risk is a public health issue of clinical importance. The prevalence of DM globally was projected to increase from 171 million in 2000 to 366 million in 2030 [1]. India has approximately 69.2 million people with DM according to IDF 5th atlas report, and it was estimated that by the year 2040, the number of people affected from DM in India will be 123.5 million [2]. The projected increase in the prevalence of DM emphasizes the importance of early detection of DM in this population.

Type 2 DM is a metabolic disorder caused by hyperglycemia or altered glucose homeostasis, where prevention strategies become highly relevant by monitoring the high-risk

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group where there is high susceptibility for developing type 2 DM. Certain modifiable and non modifiable risk factors may lead to development of type 2 DM. Overweight, sedentary lifestyle, obesity, and high blood pressure are the modifiable factors whereas age, family history, and ethnicity are the non modifiable risk factors which promote type 2 DM. Diabetes along with hypertension are major risk factors for cardiovascular diseases. The cost of treating these risk factors are causing severe economic strain to many economies [3–5]. Type 2 DM is triggered by genetic susceptibility and familial aggregation in several populations [6, 7]. Familial clustering of type 2 diabetes is well known and high in Asians, Indians, and Europeans [8, 9].

The risk factors for DM may be transmitted from parents to offspring through common lifestyles, genetic profiles, epigenetics, and other factors [10]. The risk due to family history reflects shared environmental and behavioral risk factors and their interactions with genes as shown by the strong familial aggregation [11]. Family history, being an established risk factor, increases the risk approximately two to four times in people with positive family history than people with negative family history [12, 13]. The risk even more increases with the number of first-degree relatives with type 2 DM. Risk of diabetes increases with the extent of DM in previous generations.

It was reported that offspring of diabetic parents develops DM at a younger age than their parents [13, 14]. Familial aggregation in type 2 DM in Indian population differs in several aspects from that noted in western countries. Therefore, family history may be useful to identify people at high risk and helps to target for life style modification through intervention among families which might reduce the risk of diabetes or at least delay the onset of diabetes. Thus, the current study was aimed to see the transmission patterns of type 2 DM in South Indian population.

Materials and methods

This was a cross-sectional study conducted among subjects registered in a tertiary care center for diabetes in South India, Chennai between June 2017 and May 2018. A total of 3093 subjects (M:F; 2044:1049) aged ≥ 15 years were selected for this study. All the subjects included in the study are type 2 DM patients and are currently taking anti diabetic medications and/or insulin. The study program was reviewed and approved by the ethical committee of the institution. Written informed consent was obtained from all the subjects.

Demographic and anthropometric details

We developed a well-designed questionnaire consisting of sociodemographic details, details on family history of diabetes, anthropometric details, lab investigations, treatment details, and age at onset of DM. Demographic data included all information about age, sex, height, and weight. BMI was calculated. Family history of diabetes was collected from the subjects, and presence or absence of DM in the first-degree relatives of the subjects (including father, mother, siblings, and children) was recorded. The analysis of occurrence of DM among the spouse was also undertaken. The presence of diabetes in a family member was recorded as positive if that member was on oral hypoglycemic agents or insulin or the diagnosis had been confirmed based on the investigations documented at the center or elsewhere. Subjects who failed to provide any information on family history, who did not wish to specify or refuse to answer, or believed to be uncertain about their family history were excluded from the study.

Study groups

The subjects are divided into three groups based on the family history risk categories maintained as registries. Group 1 had no parents with diabetes history but diabetes was observed in first-degree relatives (sister, brother, children) (NPDR) (n = 1414) (M:F; 928:486). Group 2 had one parent with diabetes either father or mother (OPDR) (n = 1216) (M:F; 808:408). Group 3 had conjugal parents with diabetes history where both parents (father and mother) had diabetes (CPDR) (n = 463) (M:F; 308:155).

Laboratory investigations

The laboratory investigations such as blood glucose (fasting and post prandial or OGTT), glycated hemoglobin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, urea, and creatinine are recorded. Diagnosis of diabetes was confirmed based on the history of treatment or by the results of OGTT. All the biochemical investigations were done in fully automated biochemistry analysers using standard methods in NABL-accredited laboratory.

Statistical analysis was done by SPSS, (version 20) software. Mean and standard deviations are reported for continuous variables; number and percentages are reported for categorical variables. Students t test or ANOVA or chi-square test was used as relevant to determine the significant difference between the groups. A p value of < 0.05 was considered as statistically significant.

Results

A total of 3093 subjects were included in this study, of which 66.1% were men and 33.9% were women. Table 1 shows the genderwise comparison of the biochemical and anthropometric details of the study subjects. Age was similar. Women had

Table 1 Genderwise comparison of the anthropometric and biochemical details of the study subjects

Parameters	Men $n = 2044$	Women $n = 1049$	p value
Age (years)	53.9 ± 11.3	53.3 ± 11	0.16
BMI (kg/m^2)	26.8 ± 4.2	28.2 ± 5	< 0.001
Duration of DM (years)	9.4 ± 7.8	8.9 ± 7.4	0.095
Plasma glucose (mg/dl)			
Fasting	166 ± 68	173 ± 72	0.01
PP	263.6 ± 95.8	264 ± 99.3	0.855
GTT Plasma glucose (mg/dl)			
Fasting	136 ± 65	116.5 ± 39.2	0.048
1 h	260.6 ± 108.4	224.3 ± 80	0.032
2 h	231 ± 129	201 ± 98.5	0.137
HbA_1c (%)	8.2 ± 1.9	8.4 ± 2.0	0.089
Urea (mg/dl)	25.5 ± 12.2	24.1 ± 14.2	0.016
Serum creatinine (mg/dl)	1.1 ± 0.3	0.9 ± 0.4	< 0.001
Total cholesterol (mg/dl)	169.8 ± 44.7	179 ± 45.4	< 0.001
Triglycerides (mg/dl)	149.7 ± 141.3	139.2 ± 71.5	0.069
HDL cholesterol (mg/dl)	39 ± 8.4	43.7 ± 10	< 0.001
LDL cholesterol (mg/dl)	100.3 ± 30.2	104.4 ± 31.3	0.004

Values are mean ± SD

BMI, body mass index; *PP*, post prandial; *HbA_1C*, glycosylated hemoglobin; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *SD*, standard deviation

significantly higher BMI than men ($p < 0.001$).Mean HbA1c was similar when compared between men and women. Total cholesterol levels were significantly higher in women as compared to men ($p < 0.001$).

The parental transmission of diabetes to offspring is shown in Table 2. In group 2, (i.e., one-parent diabetes registry) genderwise comparison showed higher transmission of diabetes from mothers than fathers. In particular, women had more maternal history of diabetes than paternal history [(58.1 vs 41.9%) ($p < 0.001$)]. However, men also had slightly higher maternal transmission but it was statistically non significant. Excess maternal transmission was also observed when group 2 and group 3 (conjugal diabetes registry) subjects were analyzed separately. The inheritance between maternal versus paternal history of diabetes among the subjects with positive family history of either one or two parent diabetes was found to be (65.8% vs 60.6%) ($p < 0.001$) respectively. Thus, maternal inheritance of diabetes was found to be more dominant than paternal history in both men and women; however, there was statistically significant difference in women proving women with maternal history of diabetes are at high risk for developing diabetes.

Table 2 Parental transmission of diabetes to offspring in group 2-(one parent diabetes registry)

	Father with DM 555 (45.6)	Mother with DM 661 (54.4)	p value
Men	384 (47.5)	424 (52.5)	0.164
Women	171 (41.9)	237 (58.1)	< 0.001

Values are n (%)

Table 3 shows the genderwise comparison of familial aggregation among the study subjects. The comparison of the history of diabetes in siblings showed that in men, the number of brothers affected by diabetes was higher when compared with the number of sisters affected with diabetes. The percentage of affected brothers versus sisters in men was (78% vs 45.7%; $p < 0.001$) whereas in women, the number of sisters affected by diabetes was higher than the number of affected brothers; the percentage of affected sisters versus brothers in women was (70.3% vs 29%; $p < 0.001$) which proved to be statistically significant. The gender-specific familial aggregation was noted. The history of diabetes in spouse of the study subjects showed that in men, the percentage of their spouse affected was 12.9% whereas in women, the percentage of their spouse with diabetes was 26.5%. Women had 10% of their children affected with diabetes and in men, 4.6% of their children were found to have diabetes.

Table 4 shows groupwise comparison of the characteristics according to family registries. There was a significant difference noted in the age and BMI of the study subjects when compared between the groups. Mean duration of diabetes was similar and mean HbA1c was also similar in the groups. Table 5 shows the groupwise comparison (group2 vs group3) of mean age at onset of diabetes among the study subjects with the mean age at onset of their parents. In group 2, the parental age at onset of diabetes (father vs mother) was 51.6 ± 12.3 vs 53.1 ± 11.9 years respectively. The mean age at onset of diabetes in study subjects of group 2 was 42.6 ± 10 years; whereas in group 3, parental age at onset of diabetes (father vs mother) was 50.3 ± 11.3 vs 50.5 ± 10.4 years respectively. The mean age at onset of diabetes in study subjects of group 3 was 40.1 ± 10 years ($p < 0.0001$).Both in group 2 and group 3 study subjects, the mean age at onset of diabetes was lower in the offspring than the mean age at onset of diabetes in their parents at least by a decade. The age at onset of diabetes in the

Table 3 Genderwise comparison of familial aggregation among the study subjects: values are n (%)

	Men n (%)	Women n (%)	p value
H/O diabetes in brothers	1593 (78)	480 (45.7)	< 0.001
H/O diabetes in sisters	594 (29)	738 (70.3)	< 0.001
H/O diabetes in spouse	264 (12.9)	278 (26.5)	< 0.001
H/O DM in male children	63 (3.1)	61 (5.8)	< 0.001
H/O DM in female children	30 (1.5)	44 (4.2)	< 0.001

Table 4 Groupwise comparison of characteristics according to family registries

Parameters	Group1 NPDR $n = 1414$	Group 2 OPDR $n = 1216$	Group3 CPDR $n = 463$	p value
Age (years)	56.5 ± 10.9	52.1 ± 10.8	49 ± 10.5	0.001
BMI (kg/m^2)	26.9 ± 4.5	27.3 ± 4.5	28.2 ± 4.6	< 0.001
Duration of DM (years)	9.2 ± 7.5	9.4 ± 8.0	8.6 ± 7.4	0.208
Plasma Glucose (mg/dl)				
Fasting	166.3 ± 69	168.3 ± 68.6	176.4 ± 73	0.034
PP	263.3 ± 97.4	263.5 ± 95.7	266.7 ± 99.4	0.808
GTT plasma glucose (mg/dl)				
Fasting	133.3 ± 58.1	128.4 ± 64.2	122.2 ± 44.8	0.698
1 h	261.7 ± 106.1	240 ± 100.1	236.5 ± 90	0.378
2 h	236 ± 127.3	211 ± 115	206.3 ± 114.5	0.401
HbA_1c (%)	8.3 ± 2.0	8.3 ± 1.9	8.5 ± 1.9	0.163
Urea (mg/dl)	25.7 ± 14.6	25 ± 11.8	23.2 ± 9.7	0.001
Serum creatinine (mg/dl)	1.1 ± 0.4	1.1 ± 0.3	1.0 ± 0.3	0.044
Total cholesterol (mg/dl)	172.1 ± 43	171.7 ± 45.4	178 ± 50	0.084
Triglycerides (mg/dl)	141.5 ± 90.1	146 ± 140.1	159 ± 151.7	0.093
HDL cholesterol (mg/dl)	40.7 ± 9.2	40.5 ± 9.2	40 ± 9.2	0.084
LDL cholesterol (mg/dl)	101.2 ± 29.4	100.8 ± 31	105.6 ± 32.8	0.043

Values are mean ± SD

BMI, body mass index; *PP*, post prandial; *HbA_1C*, glycosylated hemoglobin; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *SD*, standard deviation

offspring of conjugal parents diabetes registry (group 3) was much earlier as compared to offspring of one parent diabetes registry (group 2) (40.1 vs 42.6 years; $p < 0.001$).

Discussion

Family history of diabetes is a well-known risk factor, and familial clustering of type 2 DM is high in Indian population [8, 9, 15]. The present study revealed that maternal influences may play an important role in the development of DM.

Table 5 Age at onset of diabetes in study subjects (group2 vs group3)

Age at onset of DM	Group2 $n = 1216$	Group3 $n = 463$	p value
Fathers	51.6 ± 12.3	50.3 ± 11.3	0.083
Mothers	53.1 ± 11.9	50.5 ± 10.4	< 0.0001
Study subjects	42.6 ± 10	40.1 ± 10	< 0.0001

Values are mean ± SD

Mothers with diabetes contributed more than fathers with diabetes to the risk of development of type 2 DM in the offspring. Several studies have shown an excess of maternal transmission of diabetes, reported in different ethnic groups and populations with varying frequencies [6, 16, 17]. In the current study, women had higher BMI than men and noted an increase of BMI with the degree of positive family history of diabetes thus showing a possibility that BMI might have influenced the findings. High BMI observed in this study both for genderwise and groupwise comparison (BMI > 25 kg/m^2) showed that obesity is a major risk factor for diabetes and it also clusters in families.

Many studies suggested that offspring whose mothers had diabetes are more likely to develop diabetes compared with offspring whose fathers had diabetes [18–20]. The San Antonio Heart Study reported that the mother-daughter transmission was more common than the mother-son transmission [21]. But, Kim et al. reported that there is a lack of excess maternal transmission of type 2 DM in Korean population. Offspring with maternal diabetes showed no increased risk for DM when compared with those with paternal diabetes

[22]. In the Framingham population, maternal and paternal diabetes conferred equivalent risk for occurrence of type 2 DM in the offspring [12]. Similarly, Lee et al. suggested that both maternal and paternal factors may be implicated in the development of type 2 DM in the Chinese population [7].

The French DESIR (Epidemiological study on Insulin Resistance Syndrome) study stated a strong relationship between familial diabetes and incident diabetes in women but not in men [23]. In the present study, for women the risk of DM was strongest for transmission of DM from mothers,whereas the risk was also high in men but failed to reach statistical significance. In contrast to the present study, finding one of our previous studies conducted two decades ago in the same population of South India showed an absence of excess maternal transmission [15] where the interpretation of results may be varied by the methodology used, and the contributing factor to the current study may be the huge sample size which is threefold higher than the previous study. This proved to be a potential strength incomparable to the previous study. Certain genetic studies revealed that mutation in the mitochondrial DNA (mt DNA) could amount for this phenomenon of maternal mode of inheritance [24, 25].Few other studies from South India also showed that there is an excess of maternal transmission, and hence maternal history of diabetes should be considered as a more predominating risk factor [26, 27].

Studies have reported that there is an early onset of diabetes among subjects with positive family history compared with subjects whose parents are without diabetes [28–30]. Family history risk categories were found to have significant association with prevalence of DM in Chinese population [30]. In the present study also, we compared the age at onset of diabetes in subjects with one parent having diabetes and conjugal parents having diabetes and found that the mean age at the onset of diabetes in the offspring with positive family history was a decade earlier than the mean age at onset of diabetes in their parents. Similar finding was reported by Bener et al. and Ramachandran et al. where the age at onset of diabetes was lower in the offspring than in their parents at least by a decade [16, 31]. The lower age at onset of DM in the offspring implies that the subjects developed DM in most productive years of their life. The chance of developing complications is high among these subjects.

The present study has also shown a scope towards gender specificity observed with men having more number of brothers affected with diabetes and women having more number of sisters affected with diabetes. The history of diabetes in siblings also showed a strong association in the transmission of diabetes. The gender specificity observed shows the transmission pattern was more towards brother, if the proband is a male offspring and more towards sister if the proband is a female offspring. So, siblings history of diabetes to be considered to reduce the risk for other offspring of parents with diabetes. Special interventions should be planned targeting these susceptible individuals through modification of risk factors of diabetes. The first-degree relatives of subjects with diabetes have a fivefold risk of developing diabetes. In the Chin-Shan community cardiovascular cohort study, it was observed that sibling history is more important than parental history for diabetes risk [32]. In this study too, the risk of diabetes in siblings was higher, and the differential result observed in this study was the gender specificity where women had more number of sisters affected and men had more number of brothers affected with diabetes. The sibling pairs have higher shared environmental factors than parent offspring pairs, and some common environment in young childhood has been postulated to be associated with future adult disease [33]. The strength of the study is the large sample size whereas the limitation of the study was that it is a hospital-based study and the results may not be applicable to the general population.

Conclusions

In conclusion, our study findings showed an excess of maternal transmission of type2 DM in particular to women suggesting that women with maternal history of diabetes and also gender-specific siblings are at high risk of developing type 2 DM. Men had more number of brothers affected and women had higher percentage of sisters affected by diabetes. The mean age at onset of diabetes in subjects with a history of diabetes in their parents was a decade earlier than the age at onset of diabetes in their parents. The findings may lead to identify a person at risk and motivate for lifestyle changes. The policy makers can plan primary prevention programs for these high-risk groups in the future based on the current study findings. Family history may serve as a useful tool for educating individuals in routine clinical practice. Larger multicentric studies are necessary to reaffirm these findings and also to understand the interplay between BMI and family history of diabetes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate Ethical clearance was obtained from the Institutional Review Board (IRB) of the hospital. Purpose and significance of the study were explained and informed consent was obtained from all individual subjects who participated in the study.

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ORIGINAL ARTICLE

BDNF is obverse to oxidative stress (adenosine deaminase and nitric oxide) in type II diabetes mellitus

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Abstract

Aim The relational analysis of adenosine deaminase (ADA), nitric oxide (NO), BDNF (brain-derived neurotrophic factor), and TP (total protein) is accomplished by comparing these parameters with glucose levels of healthy and type II diabetes mellitus people. Type 2 diabetes (T2DM) is associated with impairment in many domains of cognitive function which may result from reduced BDNF. ADA is an important enzyme that plays a relevant role in purine and DNA metabolism, immune responses, and peptidase activity and for modulating the bioactivity of insulin. Nitric oxide is associated with loss of normal cellular function and increases the generation of nitric oxide synthetase products like nitroxyl (NO-), peroxynitrite (OONO-), and *S*-nitrosothiol (RSNO).

Method In our study, a group of one hundred adult patients of either sex who had a history of not less than 6 years of diabetes mellitus and an equal number of healthy non-diabetics was selected as controls, respectively.

Results The results of the parameters were analyzed using the SISA software and the correlation between the parameters was retrieved and represented graphically. A significant increase in adenosine deaminase activity and nitric oxide levels was observed in diabetic subjects when compared with that in controls. A significant decrease in total protein concentration and BDNF was observed in diabetic subjects when compared with that in controls. The results suggest that the increase in the glucose level has contributed to an increase in the inflammation factor ADA and oxidative stress factor NO and decrease in the total proteins especially BDNF, a neuron sentinel.

Keywords BDNF · ADA · NO · TP · Diabetes mellitus

Introduction

Diabetes mellitus

Diabetes mellitus is a long-lasting metabolic illness characterized by variations in carbohydrates, proteins, and lipid metabolism resulting from functional or structural changes in insulin secretion, insulin action, or both [1]. Worldwide, diabetes is estimated to affect 387 million Indians, which is increasing dramatically. The maximum number of diabetes people is observed between 40 and 59 years of age [2]. In India, about 63 million people are suffering from diabetes (Diabetes Foundation India). Few survey studies also indicate that the number of diabetics in East and West Godavari districts of Andhra Pradesh is approximately nine lakhs.

In T2DM (type II diabetes mellitus), when a meal is ingested by a person, blood glucose or sugar level rises which stimulates the insulin secretion that transports excess glucose to muscles and fat tissues and stored as glycogen and fats. Under the starving conditions, the liver transforms glycogen to glucose that is used by the brain. The insulin inhibits the secretion of glucagon and lowers serum fatty acid concentration declining the glucose production [3], besides the glucose storage. The intracellular hypoglycemia and extracellular hyperglycemia are the results of reduced glucose uptake by tissues which are formally called insulin resistance. The intracellular hypoglycemia causes diabetic ketoacidosis via glucogenesis and gluconeogenesis that eventually leads to fat breakdown and decreased protein synthesis and gammaglobulins, causing impaired wound healing, polyphagia, and

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cachexia. The extracellular hyperglycemia leads to osmotic dieresis and hyperglycemic coma [4]. The blood glucose is a measure of FBS (fasting blood sugar). The person is said to be normal if the FBS is in the range of 70–99 mg/dl. Diabetes in the long run has many complications like diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hypertension, and cardiac problems.

BDNF

The BDNF (brain-derived neurotrophic factor) protein is synthesized in the brain cavities and transferred to other peripheral parts of the body like saliva, blood circulation, and cerebrospinal fluid. It plays an important role in neuronal activity and neuron survival and regeneration. BDNF is a family member of the neurotrophic factor, which is essential in playing a key role in regulating growth, survival, and maintenance of neurons, followed by learning and memory [5]. Evidence proves that patients suffering from major depression have lower levels of serum BDNF than normal control subjects [6].

In animals, BDNF is related to insulin resistance. BDNF eventually reduces food intake by controlling the appetite of the organism. It also lowers blood glucose levels in obese diabetic mice [7, 8]. The hypoglycemic effect of BDNF cannot be endorsed solely to find the hypophagic effect of BDNF, because BDNF administration has beneficial effects on glucose homeostasis. The BDNF improves insulin resistance in db/db mice even when food intake is uncontrolled in mice [7, 8]. This suggests that besides the role of diet in controlling diabetes, the BDNF could improve the insulin resistance to control diabetes. Studies on BDNF-deficient mice (Bdnf +/−) explain the role of BDNF in metabolism. BDNF enhances insulin sensitivity [7]. Furthermore, BDNF activates several signaling pathways like phosphatidylinositol-3 kinase/Akt and insulin metabolism [9]. The BDNF protein is necessary for the neuronal and also for improving insulin resistance. If the BDNF protein is reduced, the onset of diabetes-associated disorder initiates i.e. diabetic neuropathy.

Adenosine deaminase

Chronic hyperglycemia is associated with oxidative stress and chronic low-grade inflammation which is said to play a vital role in the pathogenesis of type 2 diabetes mellitus (T2DM) [10], which is a forerunner of cardiovascular disease (CVD). Adenosine deaminase (ADA) is recommended to be an important enzyme for modulating the bioactivity of insulin [11]. Immunological disturbances of cell-mediated origin are believed to initiate from T lymphocyte dysfunction. Recent in vitro studies implicated that in type 2 diabetes mellitus, inappropriate immune responses may result from the defects in the action of insulin that is required for the function of T lymphocytes [12]. Adenosine is found to exert an anti-inflammatory effect and, therefore, ADA may regulate the inflammatory response [13]. It acts as an enzyme of purine metabolism which converts purine nucleoside adenosine to inosine in virtually all the cells, by a process of deamination. ADA is an important enzyme that plays a relevant role in DNA and purine metabolism, peptidase activity and immune responses, and modulating the insulin bioactivity. The use of adenosine deaminase is a cost-effective process and the efficient exploitation of this strategy may help in better establishing this enzyme as a good marker for assessing CMI in diabetic individuals. The higher ADA activity will enhance insulin resistance in the tissues, and glucose uptake into cells is reduced; thus, if ADA activity is suppressed, insulin sensitivity may be improved and cellular proliferation, inflammation, and T cell activity (all of which are associated with the pathophysiology of insulin resistance) can be altered [14]. The elevated adenosine deaminase activity is an important indicator in the increased insulin resistance and immunopathogenesis of type 2 diabetes mellitus [3]. The increased insulin resistance would increase the dependence of a person on medication for controlled maintenance of diabetes mellitus.

Nitric oxide

Insulin resistance and diabetic complications like heart attack are due to the increase in the reactive oxygen and reactive nitrogen species (ROS and RNS) [15]. These are the negative modulators of cellular signaling of insulin. Hyperglycemia directly or through the generation of advanced glycated end products (AGEs) activates PKC (protein kinase C), which increases the flux of glucose through the polyol pathway and the hexosamine pathway leading to the oxidative stress [4] that further activates endothelial dysfunction [16]. Among all complications, endothelial dysfunction is a common problem in all diabetic patients [15] that would lead to cardiovascular diseases [17].

Nitric oxide is associated with loss of normal cellular function and increases the generation of nitric oxide synthetase products like nitroxyl (NO-), peroxynitrite (OONO-), *S*-nitrosothiol (RSNO) and superoxide overproduction. NO interacts with O_2^- leading to NO inactivation and production of peroxynitrite, which post transcriptionally modifies proteins and negatively affects their function increasing cell permeability. Polymerase activation (adenosine diphosphate ribose) initiates the pathway leading to the development of diabetes-related complications [18] like cardiovascular diseases.

Evidence derived from experimental models of diabetes suggests that an inactivation mechanism of nitric oxide is increased by either oxygen-derived free radicals [19] or advanced glycosylation end products [20]. Oxygen radicals are known to mediate the breakdown of endothelium-derived nitric oxide [21], which is produced by a number of reactions in diabetes mellitus people that include glucose auto-oxidation,

non-enzymatic protein glycation, and cyclooxygenase catalysis [19]. Certainly, a number of investigators have reported that the scavengers of oxygen radicals improve endothelium-dependent relaxation in diabetic animals both in vitro [22–25] and in vivo [26].

Total protein

Diabetes is accompanied by defects in insulin metabolism. Protein stimulates the insulin secretion. Arginine, lysine, leucine, and phenylalanine are the most effective amino acid secretagogues. There are two mechanisms by which protein can stimulate insulin secretion. The first is by direct influence; insulin secretion is facilitated through the absorbed amino acids on β cells of the pancreas. The amino acids contribute to the de novo synthesis of glucose via gluconeogenesis directly from which glycine and leucine together stimulate insulin release from pancreas [27]. The secondly is by indirect influence; this is facilitated through the release of intestinal incretins. These incretin hormones are released from the gastrointestinal tract in response to the food intake, which may stimulate, potentiate, and prevent the secretion of other substances that cause metabolic effects. The incretin is important in augmenting insulin secretion, as ingested amino acids cause greater insulin response than being infused [28]. By direct and indirect influence, the protein helps in the insulin secretion [29].

Materials and methods

Collection of samples

This study was approved by the mode of the Jawaharlal Nehru Technological University Ethical Committee. All the methods were performed in accordance with relevant guidelines and regulations for human subject research. Written informed consent was obtained for analysis of medical and dietary histories, blood and serum samples.

Exclusive and inclusive parameters

Participants were excluded if they (1) were pregnant, (2) had a recent viral attack, (3) had a history of organ transplantation, or (4) had an unstable clinical condition (bleeding, infection, intestinal obstruction, etc.), (5) had type I diabetes mellitus, (6) had gestational diabetes i.e. type III diabetes mellitus. Participants of age group 35–65 comprising both male and female subjects were included.

Blood samples from 100 non-diabetic, healthy people and 100 type II diabetes mellitus (under medication)–diagnosed patients were collected along with their respective case histories. The serum samples of both the fasting and postprandial blood samples were separated by centrifuging the blood collected without the addition of EDTA at 3000 rpm for 10–15 min. Serums were separated and isolated from all the blood samples. Serum was stored at − 20 °C until assay of FBS, total protein concentration, ADA levels, NO levels, and BDNF levels. The fasting blood sugar levels (FBS) were measured by a glucometer and the values were represented as pg/ml.

Total protein estimation

The total protein content of serum was estimated by the Lowry method [19]. In this, complex-forming reagents were taken: Stock solution A, 2% (w/v) Na_2CO_3 in 0.1 N NaoH; stock solution B, 1% sodium potassium tartrate in distilled water; stock solution C, 0.5% (w/v) $CuSO_4.5H_2O$ in distilled water; reagent I, 48 ml of A, 1 ml of B, and 1 ml of C; reagent II, 1 part Folin phenol [1 N] and 1 part water. Standards: A stock solution of standard protein (bovine serum albumin (BSA) fraction) containing 4 mg/ml protein is dissolved in distilled water and stored frozen at − 20 °C. Standards are prepared by diluting the BSA with distilled water as follows:

BSA protein concentration (mg/mL), 4
BSA volume (μL), 0, 200, 400, 600, 800, and 1000
Water volume (μl), 1000 800, 600, 400, 200, and 0

A total of 4.5 ml of reagent I was added to all the dilutions and incubated for 10 min. After incubation, 0.5 ml of reagent II was added and incubated for 30 min. The absorbance was measured at 660 nm by using Labindia UV 3000+ UV-Vis spectrophotometer and the standard graph was plotted. The unknown serum sample concentration is determined by taking a standard graph as a reference. The values of the total protein are represented as g/l.

Estimation of adenosine deaminase

ADA levels from serum were estimated by Giusti et al. (1974). The principle involved is that adenosine deaminase of purine salvage pathway catalyzes the hydrolytic cleavage of adenosine to inosine and NH3 (ammonia). The ammonia formed in the reaction is estimated using alkaline hypochlorite [30].

Stock solution A, 50 mM phosphate buffer (pH 6.5)
Stock solution B, 5.6 mg/ml
Stock solution C, 0.2% (w/v) ammonium sulfate in phosphate buffer
Stock solution D, 5 mg/ml sodium nitroprusside in phenol
Stock solution E, 2 M hypochlorite solution in 1 N NaOH

The assay was performed by considering reagent blank, standard, sample blank, and sample in a consecutive manner as shown in Table 1. The absorbance was measured at 635 nm

by using the Labindia UV 3000+ UV-Vis spectrophotometer. The activity of ADA is expressed in units/liter, i.e., 1 μl mol of ammonia released from the substrate in 1 min at 37 °C in 1 l of assay material (μ mol/min/l = units/l).

Calculation:

$$\text{Volume activity} = \frac{\text{Sample O.D} - \text{Sample blank O.D}}{\text{Standard O.D} - \text{Reagent blank O.D}} \times (50)$$

Estimation of nitric oxide

The nitric oxide (NO) levels were estimated from serum samples by standard method of Griess reagent [31]. Nitrate and nitrite concentration present in the reaction solution can be determined by using Griess reagent in which NO reacts with 1% sulfanilamide in 5% phosphoric acid, naphthalene ethylenediamine, dihydroxy chloride, forming chromophore.

Stock solution A, 70% sulfosalicylic acid
Stock solution B, 10% NaOH
Stock solution C, 5 mM Tris HCl, pH 9.0
Reagent I, 0.3% *N*(1-napthyl) ethylene diamine dihydrochloride (light-sensitive)
Reagent II, 3% sulfanilamide in 1 N HCl
Griess reagent, Mix reagent I and II in equal volume (light-sensitive).

One milliliter of serum and 0.1 ml of sulfosalicylic acid were taken and the mixture was vortexed for 30 min, followed by centrifugation at 3000 rpm for 20 min. Two hundred microliters of the supernatant was aspirated and 30 μl of 10% NaOH in 300 μl of tris HCl buffer (pH at 9.0) was added. Finally, 530 μl of Griess reagent was added and incubated for 10 min in darkness. The absorbance was read at 540 nm against water blank using the Labindia UV 3000+ UV-Vis spectrophotometer. The values of the total protein are represented as units/l.

BDNF estimation by ELISA

The BDNF E_{max}® ImmunoAssay System is designed for the sensitive and specific detection of BDNF in an antibody sandwich format. In this format, flat-bottom 96-well plates are coated with anti-BDNF monoclonal antibody (mAb) to bind soluble BDNF. The captured BDNF binds the second, specific BDNF polyclonal antibody (pAb). After washing, the amount of specifically bound pAb is detected using a species-specific anti-IgY antibody conjugated to horseradish peroxidase (HRP) as a tertiary reactant. Unbound conjugate is removed by washing, and following incubation with a chromogenic substrate, a color change is measured. The amount of BDNF in the test solution is proportional to the color generated in the oxidation-reduction reaction. BDNF protein levels from the serum samples were measured by ELISA [32].

Serums from non-diabetic and diabetic people of equal volume are taken and BDNF is performed using enzyme linked immunosorbent assay kit (ELISA) (Promega Emax ImmunoAssay system). The BDNF was quantitatively determined according to the manufacturer's instructions.

Coating antibody (per plate)

Ten microliters of anti-BDNF mAb was mixed with 9.99 ml carbonate coating buffer (pH 9.7). One hundred microliters of coating antibody is added per well and incubated overnight at 4 °C without shaking. After incubation, the coating buffer is emptied from all the wells and washed once with TBST (a mixture of tris-buffered saline (TBS) and polysorbate 20 (Tween 20)) wash buffer.

Block and sample buffer

The block and sample 1X buffer is prepared by mixing 42.4-ml deionized water with 10.6-ml block and sample 5X buffer (containing gentamycin). Two hundred microliters of block and sample buffer is added per well and incubated for 1 h at room temperature without shaking. After incubation, the block and sample buffer is emptied from all the wells and washed once with TBST (a mixture of tris-buffered saline (TBS) and polysorbate 20 (Tween 20)) wash buffer.

Sample

Standard

BDNF standard (human recombinant BDNF at 1 μg/ml in phosphate-buffered saline 1 mg/ml bovine serum albumin) and human serum were diluted as per the diluents supplied in the kit. The BDNF standard was diluted by 1:2000 with the block and sample 1X buffer and 200 μl was added to row A of columns 11 and 12 of a 96-well plate. Later, 100 μl of block and sample 1X buffer (containing gentamycin) was added to rows B–H of columns 11 and 12. Six 1:2 serial dilutions were until the row G, whereas H is not added with BDNF standard.

Serum

One hundred microliters of 20-fold diluted human serums of both control and diabetic is loaded in the rows (A, B, C, D, E, F, G, H) rows X (1–10) columns and performed in duplicate. The plate was incubated for 2 h at room temperature with shaking. After incubation, the standard and serum dilutions are emptied from all the wells and washed 5 times with TBST (a mixture of tris-buffered saline (TBS) and polysorbate 20 (Tween 20)) wash buffer.

Table 1 Characteristics of the study population

S. No	Parameter	Sample	Minimum value	Maximum value	Mean ± Stdev
1	Total protein concentration	Control	7.01	8.20	7.51 ± 0.37
		Diabetic	0.13	5.27	2.6 ± 1.22
2	Total BDNF	Control	1550	1690	1627.26 ± 27.83
		Diabetic	561.23	614.5	593.44 ± 11.92
3	NO	Control	1.66	2.84	2.21 ± 0.31
		Diabetic	3.19	5.46	4.36 ± 0.64
4	ADA	Control	7.5	14.75	11.12 ± 1.87
		Diabetic	24.22	34.75	28.43 ± 2.61
5	Glucose (FBS)	Control	70.15	107.19	89.82 ± 6.8
		Diabetic	134	200	161.28 ± 15.57

Anti-human BDNF p^{Ab}

Twenty microliters of anti-human BDNF p^{Ab} antibody (chicken IgY in tris-buffered saline containing gentamicin) was mixed with 9.98 ml of block and sample 1X buffer (containing gentamycin). One hundred microliters of the mixture is added to all the 96 wells and incubated at room temperature for 2 h with shaking. After incubation, the anti-human BDNF p^{Ab} is emptied from all the wells and washed 5 times with TBST (a mixture of tris-buffered saline (TBS) and polysorbate 20 (Tween 20)) wash buffer.

Anti-IgY HRP conjugate

Fifty microliters of anti-IgY HRP conjugate (rabbit antibody in a stabilizing solution) was mixed with 9.95 ml block and sample 1X buffer. One hundred microliters of the anti-IgY HRP conjugate was added to each well. The plate was incubated for 1 h at room temperature with shaking. After incubation, anti-IgY HRP conjugate was emptied from all the wells and washed 5 times with TBST (a mixture of tris-buffered saline (TBS) and polysorbate 20 (Tween 20)) wash buffer.

TMB (3, 3′, 5, 5′-tetramethylbenzidine)

TMB (3, 3′, 5, 5′-tetramethylbenzidine) one solution was equilibrated to room temperature and 100 μl was added to each well as a substrate for the color development. The incubation was kept at room temperature for 10 min. The reaction was ceased by the addition of 100 μl of 1 N HCl to each well. Finally, the optical density (O.D) or absorbance was read at 450 nm within 30 min in the microplate reader. The actual concentration for all the samples was calculated using the (four) 4-parameter fit logistic (4-PL) curve. The detection limit of the BDNF ELISA kit was as précised as 19.8 pg/ml. The entire procedure was done using the Thermo Scientific Multiskan EX reader. The washes were performed by Thermo Scientific WELLWASH 4 MK 2. The values of the total protein are represented as pg/dl.

Results

The control and diabetics values for all the parameters were analyzed by simple interactive statistical analysis (SISA). The statistics for glucose and BDNF; NO, ADA, and glucose were tabulated in Table 1.

The correlation results depicted in Tables 2 and 3 explain the correlation between the different parameters in both control and diabetic samples.

Discussion

The diabetic people have many changes within their cell mechanisms that would lead to differential regulation of proteins. This paves the incidence of uncontrolled high blood glucose, high nitric oxide (NO) levels, high ADA (adenosine deaminase) levels, decline in BDNF (brain-derived neurotrophic factor) values, decline in HDL (low-density lipids), high low-density lipids (LDL), high cholesterol, high triglycerides, high lipid peroxidation, and decline in total protein (TP). These factors would lead to complications like diabetic neuropathy, cardiovascular diseases, low immunity, diabetic nephropathy, diabetic retinopathy, and diabetic coma.

Table 2 Correlation analysis of all parameters for all Control samples

	BDNF	TP	NO	ADA	Glucose
BDNF	1				
TP	0.91	1			
NO	− 0.97	− 0.9	1		
ADA	− 0.98	− 0.92	0.95	1	
Glucose	− 0.97	− 0.93	0.99	0.95	1

Table 3 Correlation analysis of all parameters for all Diabetic samples

	BDNF	TP	NO	ADA	Glucose
BDNF	1				
TP	0.78	1			
NO	− 0.81	− 0.98	1		
ADA	− 0.88	− 0.88	0.91	1	
Glucose	− 0.9	− 0.88	0.91	0.98	1

These would eventually lead to hypertension, amputations, kidney failures, blindness, cataracts, and paralysis [33].

In our study, we have focused on the parameters that play an important role in the long run of diabetes mellitus that paves a way for diabetic complications. The parameters are glucose (considering the years of onset of diabetes) for hyperglycemia and insulin resistance, ADA for inflammation, tissue damage and low immunity, NO for oxidative stress and cardiovascular diseases, BDNF for onset of diabetic neuropathy, and neurological disorders.

For this study, we have collected 100 diabetic and 100 non-diabetic blood samples. The case histories of all the 200 samples were collected. The serum and plasma were separated; and the parameters, viz., glucose (FBS), ADA, NO, total protein, and BDNF. The experimental measures of the parameters were correlated with the theoretical basis and symptoms that were observed as associated disorders (case studies).

From the experimental results, we found elevated levels of ADA in diabetic patients when compared with controls. These studies are correlated with those of Prakash et al. [3]. Their studies showed a significant ascend in the adenosine deaminase levels in diabetic subjects, compared with that in controls. The high level of plasma adenosine deaminase activity may be due to abnormal T lymphocyte response or proliferation which may focus on the mechanism involved in its release into the circulation [13]. Therefore, we report that increased activity of adenosine deaminase in diabetic patients may be due to altered insulin–related T lymphocyte function [34]. The higher ADA activity enhances insulin resistance in the tissues, and glucose uptake into cells is reduced; thus, if ADA activity is suppressed, insulin sensitivity may be improved and cellular proliferation, inflammation, and T cell activity (all of which are associated with the pathophysiology of insulin resistance) can be altered [14]. The elevated adenosine deaminase activity is an important indicator in the increased insulin resistance and immuno-pathogenesis of type 2 diabetes mellitus [3]. The increased insulin resistance would increase the dependence of a person on medication for controlled maintenance of the diabetes mellitus. The ANOVA for the ADA ($F(1,198) = 2889$, $p < 0.05$, F test value > critical value) indicated that the diabetics reported significant levels of ADA in comparison with the healthy group (control).

Similarly, in the case of nitric oxide, results are correlated with those of Ghosh et al. [35]. Their results revealed that serum of diabetics has high NO values compared with that in non-diabetics [20]. In our study, the non-insulin-dependent diabetics showed evidence of impaired response for endothelium-derived nitric oxide (released in response to methacholine) and exogenous nitric oxide donor nitroprusside [26, 36]. These results can be compared with the impaired vasodilation with acetylcholine and glyceryl trinitrate in non-insulin-dependent diabetic subjects relative to control subjects, reported by McVeigh [37]. Our study specifically confirms the impaired response to exogenous nitric oxide donors and thereby indicates the vascular defect in type II diabetes mellitus that cannot be attributed solely to abnormal endothelial production of nitric oxide [19].

Nitric oxide is associated with loss of normal cellular function and increases the generation of nitric oxide synthetase products like nitroxyl (NO-), peroxynitrite (OONO-), and *S*-nitrosothiol (RSNO) and superoxide overproduction [21–25]. NO interacts with O_2^- leading to NO inactivation and production of peroxynitrite, which post transcriptionally modifies proteins and negatively affects their function increasing cell permeability. Polymerase activation (adenosine diphosphate ribose) initiates the pathway leading to the development of diabetes-related complications [18] like cardiac vascular diseases.

Insulin resistance and diabetic complications like heart attack are due to the increase in the reactive oxygen and reactive nitrogen species (ROS and RNS) [15]. These are the negative modulators of cellular signaling of insulin. Hyperglycemia directly or through the generation of advanced glycated end products (AGEs) activates PKC (protein kinase C), which

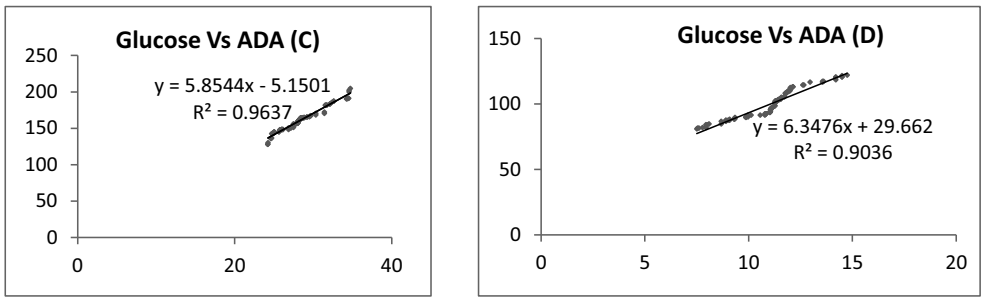

Fig. 1 Correlation of glucose and ADA for control (C) and diabetic samples (D)

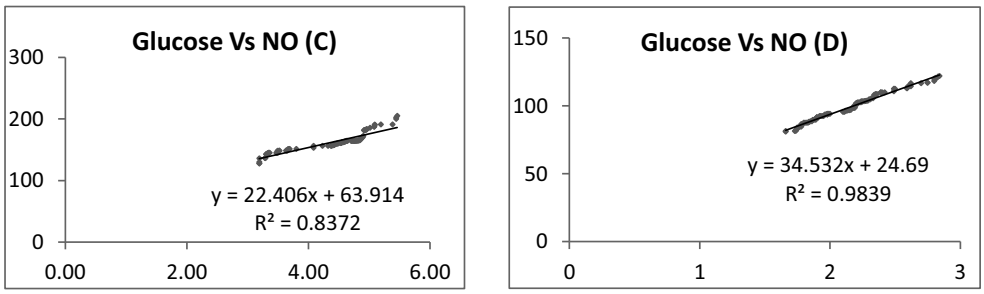

Fig. 2 Correlation of glucose and NO for control (C) and diabetic samples (D)

increases the flux of glucose through the polyol pathway and the hexosamine pathway leading to the oxidative stress [4] that further activates endothelial dysfunction [16]. Among all complications, endothelial dysfunction is a common problem in all diabetic patients [15] that would lead to cardiovascular diseases [17]. The ANOVA for the NO ($F(1,198) = 905$, $p < 0.05$) indicated that the diabetics reported significant levels of NO in comparison with the healthy group (control).

We could also find that protein levels have shown a significant decrease in diabetic individuals when compared with those in the controls. The protein declination in the serum levels is considerable and on this basis, the protein in the total body of diabetics is assumed to show peak declination [38]. This decrease in diabetic individuals will affect their metabolism [38]. The total protein in the body decreases that aims to lose body weight, body built, and strength, as proteins are the building blocks of our body. The ANOVA for the TP, ($F(1,198) = 1479$, $p < 0.05$) indicated that the diabetics reported significant levels of TP in comparison with the healthy group (control).

As protein is essential for tissue repair and muscle building [39], the proteins function as enzymes for the chemical reactions, antibodies, peptide hormones, neurotransmitter, and blood carrier proteins and be a part in the formations of muscle fibers, hair, skin, nails, etc. It is an important molecule without which the molecules like DNA, RNA, glutathione (a critical antioxidant), and creatinine (supplies energy to muscles) formation takes place. The non-essential amino acid synthesis decreases, so there would be a requirement of intake of non-essential amino acids along with the essential amino acids. The serum total protein concentration is a measure of all the plasma proteins without the clot formation factors. The plasma proteins are essential for the drug to work efficiently in the body. The drug's efficiency depends on the binding of a drug to the plasma protein. As per the obtained results, the above functions along with the action of drug are affected. Insulin action and other receptor binding activities are also affected. The glucose regulation and maintenance are disturbed, for which the blood sugar level rises. This increase in the blood sugar leads to hyperglycemia; oxidative stress; inflammation-associated disorders like retinopathy, nephropathy, and neuropathy; and decrease in life span; etc.

Similarly, from our results, we can observe that the long run of diabetes would also tend to show a declined effect on BDNF protein. The BDNF is associated with the growth, survival, and differentiation of neurons, and this decrease will lead to neurological disorders [40, 41,42]. The BDNF protein is also interlinked with glucose metabolism. Hence, BDNF protein declination would cause diabetic neuropathy [43]. The neurological disorder symptoms were observed in the patients with low BDNF protein (case history). These neurological disorders are observed in about 95% of the diabetic samples. The ANOVA for the BDNF ($F(1,198) = 116{,}579$, $p < 0.05$) indicated that the diabetics reported significant levels of BDNF in comparison with the healthy group (control).

The blood glucose level has a negative (inverse) correlation with total protein concentration and BDNF and a strong positive correlation with ADA and NO (Figs. 1, 2, 3, and 4). This can conclude that the biochemical parameters ADA, an inflammatory marker, and NO, a thrasher of normal cell functioning, will extend the sternness of type II diabetes and lead to disorders like cardiovascular problems and low immunity. The total protein concentration decreases affecting the cell metabolism and overall strength of the body, markedly the BDNF protein, which is necessary for the neurogenesis, neuronal growth, differentiation, survival, and maturation, leading to the neuronal complications such as diabetic neuropathy and less body strength.

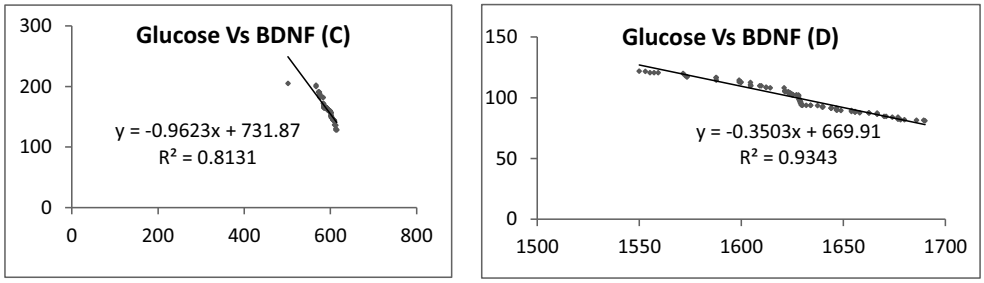

Fig. 3 Correlation of glucose and BDNF for control (C) and diabetic samples (D)

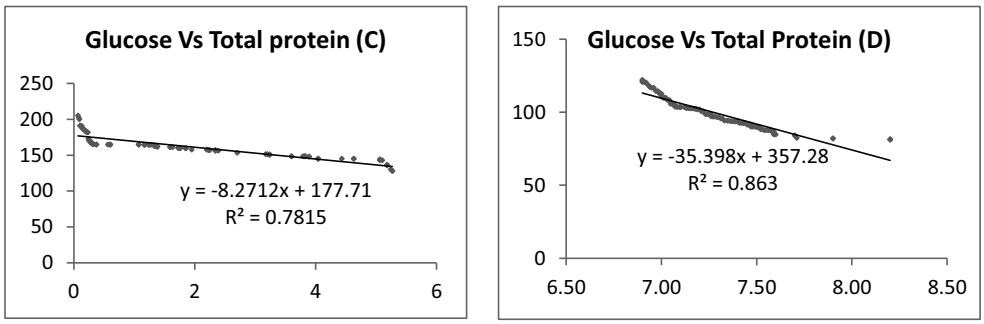

Fig. 4 Correlation of glucose and total protein for control (C) and diabetic samples (D). The glucose (mg/dl) is taken on *x* axis and total protein (mg/ml) is taken on *y* axis

From all our findings, it is revealed that the people with long run of diabetes show different disorders, from which cardiovascular diseases, low immunity, diabetic neuropathy, protein deficiencies, and hyperglycemia were more concentrated in our study. The parameters selected in the study directly influence the disorders. These observations were also correlated with the case history symptom.

From our study, it is concluded that the people with long run of diabetes are mostly affected by the abovementioned disorders. Hence, a yearly check of the NO, ADA, BDNF, glucose, and total protein would help in decreasing the frequently observed diabetic complications.

Conclusion

Our findings reveal that the blood glucose level has a negative (inverse) correlation with total protein concentration, insulin concentration, and BDNF and a strong positive correlation with ADA and NO. This can conclude that the biochemical parameters ADA, an inflammatory marker, and NO, a thrasher of normal cell functioning, can cause or extend the sternness of type II diabetes to cause diabetic complications. The decrease in the total protein concentration affecting the cell metabolism, markedly the BDNF, that helps in neurogenesis, neuronal growth, differentiation, survival, and maturation leading to the neuronal complications is associated with diabetes, categorized as diabetic neuropathy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the mode of the Jawaharlal Nehru Technological University Ethical Committee. All the methods were performed in accordance with relevant guidelines and regulations for human subject research.

Informed consent Written informed consent was obtained for analysis of medical and dietary histories, blood and serum samples.

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ORIGINAL ARTICLE

The role of osteocalcin in mechanism of Steroid induced diabetes mellitus

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Abstract

Background Steroids induced diabetes (SID), may be due to either insulin resistance (IR) or beta cell dysfunction or combination of both. Several studies have established that these effects of steroids may be mediated by an osteoblast derived protein called osteocalcin (OC). However, this effect has been described only in diabetic patients and has not been studied in SID patients.

Aim and study design A prospective observational cohort study was designed to evaluate the correlation between serum OC level and blood glucose profile, in patients on steroids.

Results Out of a total of 88 subjects who were on steroid therapy, 42(47.7%) subjects had their blood sugar levels in the diabetic range. Based on the glycemic status, subjects were divided into three groups, namely, normoglycemic, pre-diabetes and diabetes. The patients who developed SID were older than normoglycemic (mean age 43.15 vs 39.27years). The age (r=-0.105 p=0.5), BMI (r=-0.3 p= 0.07) and abdominal obesity (r=-0.32 p=0.04) were negatively correlated with serum osteocalcin in diabetes group. Serum osteocalcin level decreased as dose of steroid increased in all three groups (normogylcemic r=-0.701 p=0.004 prediabetes r=-0.3 p=0.07 diabetes -0.362 p=0.04). Fasting plasma glucose (r=-0.319 p=0.04), Fasting insulin (r=-0.10 p=0.5) and IR (r=-0.194 p=0.212) were increased with decrease in OC in patients in diabetes group.

Conclusion Decrease in serum osteocalcin level with increase in glycemic parameters in steroid induced diabetes group, point to have a new role in mechanism of steroid induced diabetes. This may be a novel target to discover drugs that can maintain the OC levels so that the effect of steroids on blood sugar level can be minimised.

Keywords Steroid-induced diabetes · Insulin resistance · Serum osteocalcin · Fasting insulin

Introduction

Since their introduction in 1950, steroids are commonly used in the treatment of both acute and chronic illnesses owing to their anti-inflammatory effects. They have many side effects, common among them hyperglycemia. The hyperglycemic effect of the steroids is one of the limiting factors to their clinical use [1, 2]

Steroids increase glucose levels in the blood by elevating glucose production in the liver and inhibiting glucose reuptake into muscles due to their effect of increasing insulin resistance (IR). They also reduce the pancreatic beta cell secretion by inducing apoptosis of beta cells. Yet, the mechanism of steroid-induced diabetes may be more complex as evidenced by newer studies [3–6].

Several studies have established that there is an endocrine function of vitamin K-dependent osteoblast-derived noncollagenous protein osteocalcin, in the regulation of blood glucose homeostasis. Steroids decrease the level of osteocalcin, which in turn contributes to the IR [7]. In type 2 diabetic patients, it was observed that lower serum osteocalcin (OC) levels were associated with increase in fasting plasma glucose (FPG), fasting insulin, and IR. [4] OC levels inversely correlated with FPG [5]. However, this effect has been

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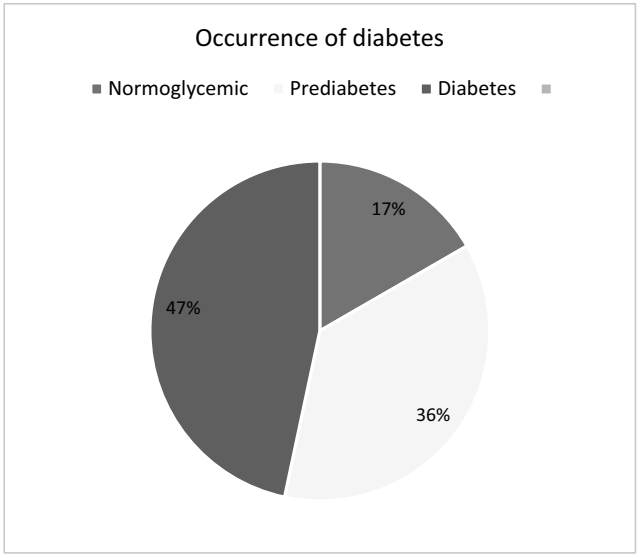


Fig. 1 Occurrence of diabetes after starting steroid therapy

described only in diabetic patients and has not been studied in steroid-induced diabetic (SID) patients. Hence, this prospective observational cohort study was designed to evaluate the correlation between serum osteocalcin level and blood glucose profile, in steroid therapy patients.

Methodology

This was a prospective observational, cohort study on nondiabetic subjects, aged between 18 and 70 years, on oral or parenteral steroid therapy for different diseases. A total of 317 patients were recruited from outpatients or inpatients in Kasturba Hospital Manipal, Karnataka from December 2015 to December 2017. Osteocalcin estimation was done in 88 patients and their data was analyzed.

Subjects who were on other drugs known to cause hyperglycemia, those who were already on steroid treatment before enrolment, those who were acutely ill, or having major organ dysfunction were excluded from the study. Osteoporosis subjects and pregnant women were also excluded.

Based on inclusion-exclusion criteria, informed consent was obtained from the patients. Detailed history of diabetes and comorbidities was recorded. All patients underwent basic anthropometry measurement including BMI and waist circumference.

In every case after detailed examination, FPG, postprandial glucose, glycated Hb, and serum osteocalcin were measured prior to starting steroids and were repeated in the first week (day 3/4) after starting steroid according to standard guidelines [8]..

The patients were divided into three groups following treatment based on ADA criteria for hyperglycemia into normoglycemic, prediabetic, and diabetic group [8].

Blood samples were collected after an overnight fasting in the morning for baseline measurement of FPG, fasting insulin, serum OC, and glycated Hb. Another sample was collected 2 h postprandial for measurement of postprandial glucose. Immediately after the collection of blood, samples were centrifuged. Analyses of FPG, glycated Hb, and postprandial glucose were done immediately. Serum samples for analysis of OC and fasting insulin were stored at – 80 °C. Same investigations were repeated except glycated Hb on 3rd or 4th day after steroid administration.

FPG and postprandial glucose (PPG) were measured by using automated auto analyzer Hitachi P800. The coefficient of variation was < 2% and < 5% for intra- and inter-batch, respectively; fasting insulin was assayed using insulin enzyme-linked immunosorbent assay kit manufactured by

Table 1 Demographic and clinical characteristics of patients across three groups ($N = 88$)

General and clinical characteristics		Normoglycemic ($n = 15$)	Prediabetic ($n = 31$)	Diabetic ($n = 42$)	p value
Age (years) (mean ± SD)		39.27 ± 12.09	43.43 ± 14.66	43.15 ± 14.67	0.6
Gender	Male (%) $n = 36$	6 (16.66)	13 (36.11)	17 (47.22)	0.44
	Female (%) $n = 52$	9 (17.3)	18 (34.6)	25 (48.07)	
Waist circumference (cm)	Male	90.56 ± 14.3	87 ± 7.19	87.17 ± 7.89	0.66
	Female	82.38 ± 7.78	87.40 ± 13.64	88.06 ± 5.86	0.18
BMI (kg/m^2)		23.68 ± 5.09	22.40 ± 4.67	25.49 ± 4.45	0.03*
Underlying disease[$]	Connective tissue and autoimmune disorder (%) $n = 57$	10 (17.5)	21 (36.8)	26 (45.61)	
	Lung diseases (%) $n = 31$	5 (16.1)	10 (32.2)	16 (51.6)	
Type of glucocorticoid used	Prednisolone (%) $n = 49$	12 (25.5)	18 (36.2)	19 (38.3)	
	Methylprednisolone (%) $n = 36$	3 (8.8)	11 (29.4)	22 (61.8)	
	Hydrocortisone (%) $n = 2$		2 (100)		
Dose of steroids(mg/kg)[#]		0.95 (0.77, 1.01)	0.97 (0.72, 2.49)	1.7 (0.94, 2.4)	0.1

*Statistically significant

[#] Median (Q1 Q3)

[$] Connective tissue and autoimmune disorder: *SLE*, systemic lupus erythematosus; *AIHA*, autoimmune hemolytic anemia; *RA*, rheumatoid arthritis; *ITP*, immune thrombocytopenic purpura

Lung disease: *ILD*, interstitial lung disease; *COPD*, chronic obstructive pulmonary disease; *BA*, bronchial asthma; sarcoidosis

Diagnostic Research Group (DRG) legal manufacturer Germany based on sandwich principle. The coefficient of variation was < 3% for intra- and inter-batch assay respectively. Serum osteocalcin levels were assayed using enzyme-linked immunosorbent assay kit manufactured by DIA source hOST-EASIA Kit Belgium with normal value of 5–25 ng/ml. Glycated Hb was measured by high-performance liquid chromatography method (HPLC) ion exchange-based method. IR was measured by HOMA 2 computerized method [9], which has been shown to correlate well with a euglycemic clamp for use in cross-sectional studies [10].

Statistical analyses

The occurrence of steroid-induced diabetes was calculated and presented in percentage. The continuous variables which were normally distributed were expressed as mean ± SD, and data which were not normally distributed were expressed as median and interquartile range. Categorical variables such as gender distribution and type of glucocorticoid were expressed in percentage. One-way ANNOVA test was used if the data was normally distributed. Kruskal Wallis test was used if data was not normally distributed. Wilcoxon signed rank test was used to compare baseline and posttreatment FPG, PPG, fasting insulin, IR, and osteocalcin concentration.

Spearman's rank correlation coefficient test was done to correlate the two continuous variables which were not normally distributed.

$p < 0.05$ was considered to be statistically significant. Statistical analysis was done by using SPSS software version 20.0.

Results

Out of 88 subjects, 42 (47%) subjects had their blood sugar in diabetic range and 31 (36%) subjects in prediabetic range after starting steroids and the remaining were normoglycemic as shown in Fig. 1.

Demographic and clinical characteristics of steroid-induced diabetes

The demographic and clinical characteristics of the study participants are presented in Table 1**.** Data is presented for all subjects ($n = 88$). Based on the glycemic status, subjects were divided into three groups, viz. normoglycemic, prediabetic, and diabetic. The patients who developed SID were older than normoglycemic (mean age 43.15 years vs 39.27 years) and similar to prediabetic group (mean age 43.43 years).The mean difference was not statistically significant across three groups. We did not find statistical significance in development of SID between male (47%) and female (48%). Mean waist circumference was not found to be statistically significant across

Table 2 Biochemical profile of patients across groups ($N = 88$)

Biochemical parameters	Normoglycemic ($n = 15$)			Prediabetic ($n = 31$)			Diabetic ($n = 42$)		
	Basal	Third day	*p* value	Basal	Third day	*p* value	Basal	Third day	*p* value
FPG (mg/dL)[$]	91 ± 10	92 ± 8	0.924	96 ± 12	110 ± 13	0.180	98 ± 21	127 ± 32	< 0.01*
PPG (mg/dL)[$]	118 ± 18	137 ± 19	0.62	114 ± 14	171 ± 49	< 0.01*	110 ± 14	213 ± 49	< 0.01*
Fasting insulin (μU/ml)[#]	7.82 (6.2, 26.3)	9.12 (6.8, 16.23)	0.765	10.2 (6.8, 16.9)	11.9 (8.8, 14.7)	0.165	12.02 (6.9, 20.9)	14.68 (9.5, 28.74)	0.137
IR[#]	1 (0.7, 3.6)	1 (0.9, 1.6)	0.3	1.5 (0.9, 2.6)	1.7 (1.1, 2.9)	0.08	1.5 (0.9, 2.5)	2.1 (1.2, 3.9)	0.08
Serum osteocalcin (ng/dL)[#]	7.7 (2.7, 10.37)	3.68 (0.7, 6.1)	0.04*	4.1 (3.29, 9.19)	1.81 (1.28, 3.67)	< 0.01*	5.27 (2.9, 8.22)	2.5 (1.14, 5.56)	< 0.01*

*Statistically significant

[#] Median (Q1 Q3)

[$] Mean ± standard deviation

FPG, fasting plasma glucose; *PPG*, postprandial glucose

Table 3 Correlation of serum osteocalcin levels with other parameters in steroid-induced diabetic patients

	Normoglycemic		Prediabetic		Diabetic	
	r value	*p* value	*r* value	*p* value	*r* value	*p* value
Age	− 0.002	0.99	− 0.26	0.15	− 0.105	0.53
BMI	− 0.018	0.99	0.126	0.5	− 0.3	0.07
Abdominal obesity	− 0.01	0.95	0.08	0.64	− 0.327	0.04*
Dose of steroids	− 0.701	0.004*	−0.3	0.07	− 0.362	0.02*
FPG	0.2	0.45	−0.18	0.31	− 0.319	0.04*
Fasting insulin	0.04	0.89	0.08	0.72	− 0.104	0.5
HOMA IR	0.05	0.88	0.277	0.14	− 0.194	0.212
HbA1c	0.178	0.6	− 0.25	0.2	0.01	0.82

r value: spearman correlation coefficient

*Statistically significant

BMI, body mass index; *FPG*, fasting plasma glucose; *HOMA IR*, homeostatic model assessment estimated IR; *HbA1c*, glycated hemoglobin

three groups. Mean difference of body mass index (BMI) was statistically significant between three groups and diabetic subjects had more BMI compared with prediabetic and normoglycemic group. The median prednisolone equivalent dose of steroid in diabetic group was higher: 1.7 (0.94, 2.4) compared with normoglycemic 0.95 (0.77, 1.01) and prediabetic 0.95 (0.72, 2.49). Fifty-seven patients had connective tissue and autoimmune disorder and 31 patients had lung diseases. Forty-nine patients were treated with prednisolone, 36 patients with methyl prednisolone, and 2 patients with hydrocortisone.

The biochemical parameters such as FPG, postprandial glucose, fasting insulin, and serum osteocalcin of the patients before and after steroid therapy are shown in Table 2**.** The mean FPG, PPG, and fasting insulin were increased in all three groups while serum osteocalcin was decreased after starting steroid therapy. We observed isolated PPG was increased in 24 (27.3%) subjects, isolated FPG was increased only in 8 subjects (9.1%), and both FPG and PPG were increased in 41 (45.5) subjects.

Correlation of serum osteocalcin with anthropometric measurement

We analyzed correlations between serum osteocalcin and anthropometric measurements including age, BMI, and abdominal obesity and various parameters related to glucose metabolism across three groups **(**Table 3). There is a weak negative correlation between serum osteocalcin and age in prediabetic and diabetic group and no correlation in normoglycemic group.

BMI and serum osteocalcin showed moderate negative correlation in diabetic group and weak positive correlation in prediabetic group and no correlation in normoglycemic group. Similarly, abdomen obesity and serum osteocalcin were significantly mild negatively correlated in diabetic group compared with weak positive correlation in prediabetic group and no correlation in normoglycemic group.

Dose of steroids was significantly negatively correlated with serum osteocalcin in all the three groups.

Subjects in prediabetic and diabetic group had serum osteocalcin reduced and FPG was increased. However, this was not seen in normoglycemic patients.

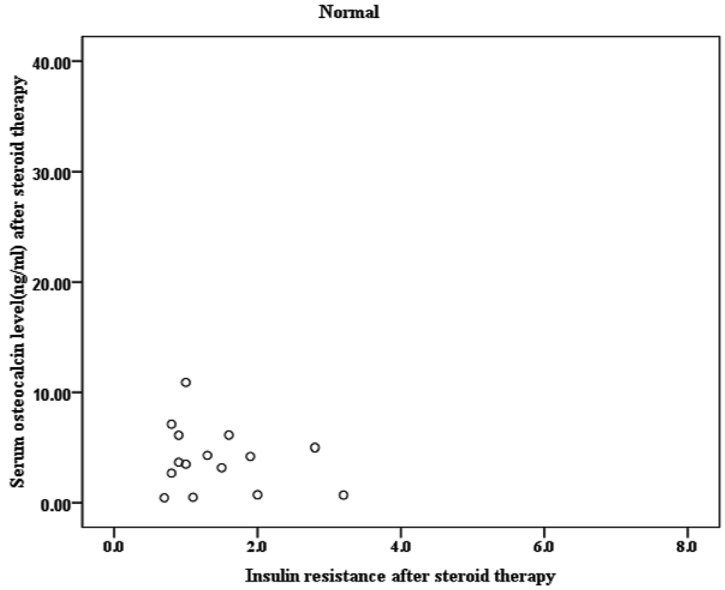
In diabetic group, fasting insulin and IR were weak negatively correlated with serum osteocalcin whereas no correlation was noticed in normoglycemic and mild positive in prediabetic group as shown in Fig. 2.

Discussion

Hyperglycemia is a common side effect seen with steroid therapy. However, the mechanism underlying this is not well understood. Recently, many studies have explained that skeletal system is one of the insulin target tissues to regulate glucose homeostasis. In 2007, Karsentry laboratory observed that osteocalcin knockout mice were glucose intolerant and insulin resistant [11]. By these discoveries, we know that OC plays a central role in the pathogenesis of diabetes. Further in 2012, Brennan-Speranza and colleagues provided evidence that the osteoblast-derived peptide osteocalcin is one of the drivers of the metabolic derangements associated with glucocorticoid therapy [3].

The occurrence of diabetes in this study was found in 47% ($n = 42$) and occurrence of prediabetes or impaired glucose tolerance in 36% ($n = 31$). The occurrence of steroid-induced

Fig. 2 Scatter plot represents correlation of serum osteocalcin and IR across three groups. Scatter plot represents IR was weak negatively correlated ($r = -0.194$, $p = 0.212$) with serum osteocalcin in diabetic group whereas no correlation ($r = 0.05$ $p = 0.88$) was noticed in normoglycemic and mild positive ($r = 0.277$, $p = 0.14$) in prediabetic group


Normal
Serum osteocalcin level(ng/ml) after steroid therapy
40.00
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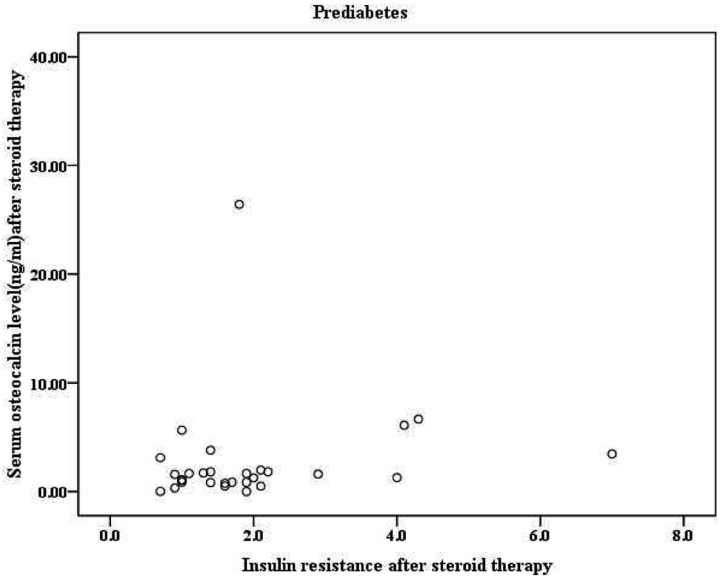
20.00
10.00
0.00
0.0
2.0
4.0
6.0
8.0
Insulin resistance after steroid therapy


Prediabetes
Serum osteocalcin level(ng/ml)after steroid therapy
40.00
30.00
20.00
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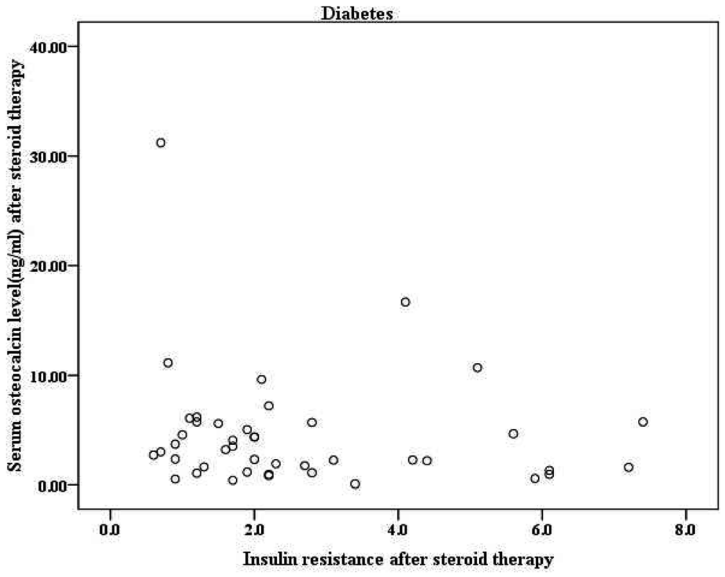
Insulin resistance after steroid therapy


Diabetes
Serum osteocalcin level(ng/ml) after steroid therapy
40.00
30.00
20.00
10.00
0.00
0.0
2.0
4.0
6.0
8.0
Insulin resistance after steroid therapy

diabetes differs across various studies from 1.5 to 47% [1]. The variability of this occurrence is due to the differences in patient population, different treatment protocols, and the definition of diabetes.

We observed 73% of subjects had increased in PPG with or without FPG compared with FPG in 54%. Normal or only mild elevation in fasting blood glucose and a large increase in postprandial glucose levels have been identified in various studies. The incidence of SID may be underestimated in studies which measured as only FPG and neglecting PPG, FPG rise is marginal [12, 13].In a study by Shanbhogue et al., it was observed that PPG increased in 89% whereas isolated FPG was raised only in 11% [14]. It has been further documented by Rao et al. that in 97% of the patients, PPG was raised with or without FPG. This makes the measurement of PPG a very important test for detecting SID [15].

Though several risk factors have been identified, these risk factors were not always constant across studies. Further, they seem to differ across different populations. These risk factors are quite unclear in Indians. [16]

In our study, patients who developed diabetes after steroid therapy were older compared with who did not develop diabetes (43.15 vs 39.27), and the same was observed in patients who has their blood sugar in prediabetic range (43.43 years). This is similar to Japanese study by Katsuyama et al. (65.2 vs 50.4) [16] and South Korean patients (65 vs 53) by Kim et al. [13] This may be due to a decrease in glucose tolerance with aging. Beta cell function also decreases with aging leading to decreased basal insulin level. In addition to these, factors such as decreased physical activity, obesity, and several medications will also increase IR in elderly.

The negative correlation between serum osteocalcin and the age and BMI of our subjects indicates that as age and BMI increase, the serum osteocalcin level decreases. Similar results were observed by Bao et al. in Chinese population [17] and Maddaloni et al. in type 1 diabetic patients [18]. However, this was different from the study by Kindbolm et al. where they observed a positive correlation with age and BMI in Swedish populations and no correlation with BMI was observed by Takashi et al. in Japanese patients [19, 20]

It is known that being overweight is often associated with impaired glucose tolerance and increased risk of developing type 2 diabetes. It is similar in our study that the group of subjects who developed diabetes following steroid therapy are overweight (mean BMI 25.49 kg/m^2) when compared with individuals who did not develop diabetes (mean BMI 23.68 kg/m^2).

Among the participants in our study, most of them are females**.** This was due to the fact that autoimmune disorders are seen most commonly in females and steroids are the primary drug of choice in most of the autoimmune disorders.

The median dose of steroids, taken by patients who developed diabetes (1.7 mg/kg prednisolone equivalent dose), was more compared with normoglycemics (0.95 mg/kg prednisolone dose) and prediabetic (0.97 mg/kg prednisolone dose). This is similar to other studies, by Donihi et al. [21] in western populations [21] and Rao et al. [15] in Indian patients.

In our study, we observed that low serum osteocalcin level was associated with increase in FPG, fasting insulin, and IR in diabetic group when compared with normoglycemic and prediabetic group. Similar studies on Caucasian and Asian populations [17, 22, 23] showed that OC levels negatively correlated with fasting blood glucose, fasting insulin, and IR in diabetic patients. However, several Chinese studies showed that OC was not related to IR [5, 21]. The reason behind IR caused by steroids was explained as chronic steroid treatment impairs insulin sensitivity in the liver, muscle, and adipose tissues. However, short-term steroid treatment decreases insulin sensitivity largely by reducing glucose disposal by muscle [24]. This loss of insulin sensitivity appears to be driven mainly by suppression of serum osteocalcin synthesis by steroids, providing a novel insight into the mechanism of steroid-induced diabetes mellitus [3, 25].

These findings have potentially important clinical implications, because for many diseases, glucocorticoids are still the first-line drug of choice. It is well known that steroids cause hyperglycemia. However, the mechanism of this is not clearly described. Since steroids suppress osteocalcin levels and decreased osteocalcin level causes IR, this may be one of the mechanisms for steroid-induced diabetes. This may be an important target for prevention of steroid-induced diabetes if future studies add to the validity of this hypothesis. Secondly, serum osteocalcin level and their correlation with glycemic patterns so far have been described only in diabetic patients. To the best of our knowledge, this may be the first study to see the correlation of serum osteocalcin levels and glycemic patterns in steroid therapy patients.

This study may have some limitations; we did osteocalcin levels on third day. Hence, we could not comment on the change in OC levels after first dose and interventional study design with measuring the osteocalcin in controlled environment would have made our study better. In the present study, many of the subjects developed hyperglycemia so there is lack of statistical power since the number of control was small.

Conclusion

As the therapeutic benefits of steroids continue to expand across medical specialties, the incidence of steroid-induced diabetes will continue to rise. Decrease in serum osteocalcin level with increase in glycemic parameters in steroid-induced diabetic group points to the new role in mechanism of steroid-induced diabetes. This may be a novel target to discover drugs that can maintain the OC levels so that the effect of steroids on blood sugar level can be minimized.

Funding information This study was financially supported by the Research Society for the study of diabetes in India (RSSDI) grants.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical clearance (IEC: 207/2015) was obtained from the Institutional Ethics Committee (IEC) of KMC and Hospital, Manipal.

Informed consent Informed consent was obtained from all individual participants included in the study.

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ORIGINAL ARTICLE

Pulmonary function tests in type 2 diabetes mellitus and their association with glycemic status and insulin resistance

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Abstract

Introduction Type 2 diabetes mellitus (T2DM) is associated with long-term complications in different organs, and this is attributable to macrovascular and microvascular changes as reported by Fowler. Pulmonary complications, however, have been poorly characterised.

Materials and methods The present study was a case–control study done at SRN Hospital, Prayagraj to correlate the pulmonary functions with glycemic status and insulin resistance in 100 patients with diabetes (cases) and compare these parameters in patients without diabetes (controls). Baseline values of fasting plasma glucose (FPG), prandial plasma glucose (PPG) and glycated hemoglobin (A1C) were significantly increased in cases as compared with controls.

Results Forced expiratory volume (FEV1) (78.71% compared with 88.15%) and forced vital capacity (FVC) (67.48% compared with 96.58%) were both decreased in cases compared with controls but as decline in FVC was more compared with FEV1; their ratio, FEV1/FVC (121.70 as compared to 90.19), was increased in cases. FVC decreased with increase in A1C values (96.2%, 84.2%, 71.2% for A1C values 5.7%, 5.7–6.4% and > 6.4% respectively). FVC was also decreased for greater values of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (98.2% for HOMA-IR < 2.5 and 74.6% for HOMA-IR > 2.5). The ratio of FEV1/FVC was more with higher values of A1C (103.3 for A1C > 2.5 and 91.1 for A1C < 2.5). FVC also decreased with increasing values of FPG (97.4%, 91.1% and 71.2% for FPG values of < 100 mg%, 100–125 mg% and ≥ 126 mg%).

Conclusion A total of 65% of patients had abnormal pulmonary function tests with predominance of restrictive pattern. This restrictive decline is significantly associated with increasing dysglycemia and insulin resistance. However, it is unrelated to levels of low-density lipoprotein (LDL) and duration of T2DM.

Keywords Type 2 diabetes mellitus · Insulin resistance · Pulmonary function tests · Forced vital capacity

Introduction

Reduced pulmonary functions have been seen in patients with diabetes [2]. Pulmonary diseases are broadly classified as obstructive and restrictive based on the pulmonary function tests (PFTs). Diabetes causes pulmonary complications by microangiopathy of the alveolar capillary network. Impairment in lung function of patients with diabetes is believed to be the consequences of biochemical alterations in the connective tissue constituents of the lung, particularly collagen and elastin, as well as microangiopathy due to the nonenzymatic glycosylation of proteins induced by chronic hyperglycemia [3]. The functional abnormalities ensuing from these changes manifest clinically by way of a reduction in elastic recoil of the lung, lung volumes and pulmonary capacity for the diffusion of carbon monoxide. There is a predominant reduction in spirometric parameters of the diabetic patients towards the restrictive pattern [4]. PFTs in type 2 diabetes mellitus (T2DM) have demonstrated varied and frequently conflicting results. Despite the unclear nature, the relationship between the diabetes and the lung function remains important because of potential epidemiological and clinical implications. The present study is an effort to correlate the pulmonary functions with glycemic status and insulin resistance in patients with

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Table 1 Comparison of pulmonary functions of cases with controls

	Cases ($n = 100$)	Controls ($n = 100$)	p value
FEV1 (% of predicted)	78.71 ± 1.51	88.15 ± 6.19	0.032
FVC (% of predicted)	67.48 ± 14.06	96.58 ± 2.58	0.001
FEV1/FVC	121.70	90.19	0.027

diabetes and compare these parameters in patients without diabetes, so that appropriate interventions could be taken up to improve the quality of life in these patients.

Materials and methods

This study was a case–control study conducted in Moti Lal Nehru Medical College Allahabad and its associated Swaroop Rani Nehru Hospital from May 2017 to August 2018. The study included 100 patients > 18 years of age, diagnosed with T2DM, attending the outpatient department of the hospital. One hundred age- and sex-matched subjects were taken as controls. Patients with acute and chronic pulmonary diseases, history of smoking for any duration, gross abnormalities of vertebral column or thoracic cage, neuromuscular diseases, those who had undergone major chest or abdominal surgeries, with ischemic heart disease and cardiomyopathies, chronic liver disease and chronic renal failure were excluded from the study. Patients underwent a morning fasting plasma glucose estimation and fasting insulin estimation after 8 h of fasting at least. Serum liver function tests (LFTs) and kidney function tests (KFTs) were also performed for all the patients. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was performed on all patients. At present, computer software is available for calculation of HOMA-IR, the value of which > 2.5 was considered as insulin resistance.

All patients underwent a series of pulmonary function tests to assess forced expiratory volume (FEV1) and forced vital capacity (FVC), and the ratio of both was calculated. It was done by using a RMS Helios 401 spirometer after explaining the procedure properly to the patient. Patients who could not exhale properly for a minimum period of 6 s were also excluded. Fasting lipid profile and A1C were performed for all the patients. In order to assess the glycemic status, cutoff values for FPG were < 100 mg/dl for normal glucose tolerance, 100–125 mg/dl for impaired fasting glucose (IFG), and ≥ 126 mg/dl for T2DM. For A1C, values < 5.7% for normal glucose tolerance, 5.7–6.4% for impaired glucose tolerance (IGT) and ≥ 6.5% for T2DM were considered.

Baseline characteristics were compared between both the groups. Patients were sub-classified into different groups on the basis of values of A1C, FPG, HOMA-IR, LDL and duration of diabetes. FEV1 and FVC were calculated, and FVC and ratio of FEV1 to FVC were compared in relevant groups.

Spirometer model, RMS 701 with Helios software (Recorders and Medicare Systems, Chandigarh) was used for PFTs. Blood glucose was determined by glucose oxidase method, and A1C level was assessed by using glycohemoglobin HbA1 test kit (fast ion exchange resin separation method). Statistical analysis was performed using Statistical Package for Social Science software (SSPS version 20.1). The numerical data was compared using two tailed Student's t test. The level of significance was considered $p < 0.05$. Prior to the test, all the subjects (control and patients) underwent a detailed history taking, general physical examination and systemic examinations.

Results

A total of 100 cases and 100 age- and sex-matched controls were analysed. Results showed that 65% patients had abnormal PFTs as shown in Fig. 1. There was a significant reduction in FEV1 (78.71 ± 1.51 in cases compared with 88.15 ± 6.19 in cases) and FVC (67.48 ± 14.06 in cases compared with 96.58 ± 2.58 in controls). The reduction in FVC was more compared with FEV1 and as a result, the FEV1/FVC ratio (121.70 in cases compared with 90.19 in controls) was increased significantly suggesting restrictive pathology as shown in (Table 1) and Fig. 2.

For three subgroups based on FPG values (< 100 mg%, 100–125 mg% and ≥ 126 mg%), the values of mean FVC

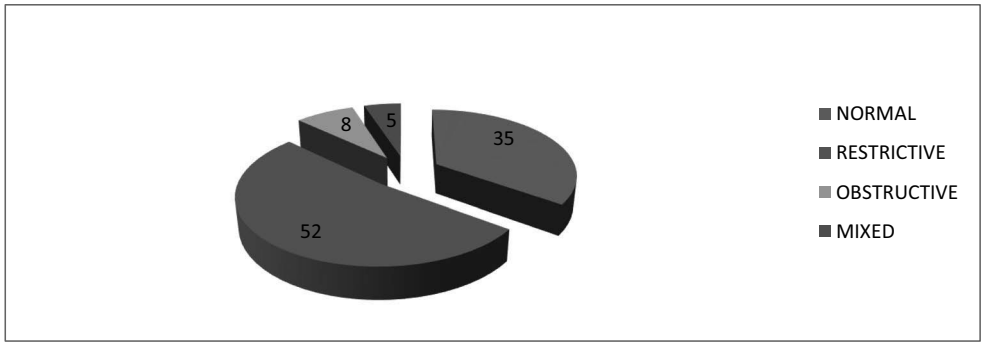

Fig. 1 Ventilatory pattern in patients with diabetes

Table 2 : Correlation of FVC with FPG, A1C and HOMA-IR

FPG (mg%)					A1C (%)				HOMA-IR		
Values	< 100	100–125	≥ 126	*p** value	< 5.7	5.7–6.4	> 6.4	*p** value	≤ 2.5	> 2.5	*p* value
FVC	97.4	91.1	71.2	0.021	96.2	84.2	72.1	0.019	98.2	74.6	0.037

*p** value: *p* value calculated for the first and last group

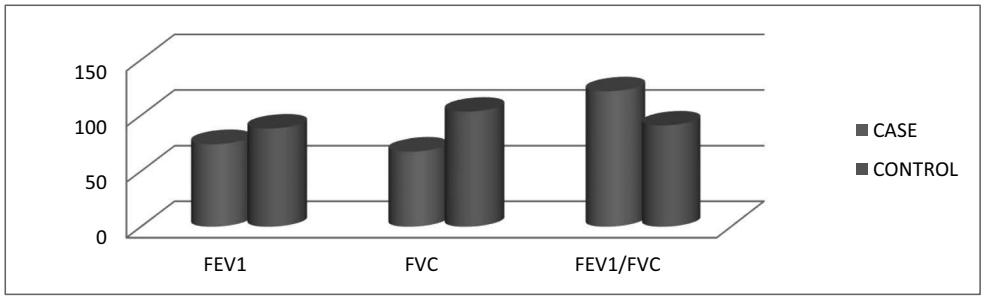

Fig. 2 Comparison of pulmonary functions of cases with controls

declined progressively (97.4%, 91.1%, 71.2%), respectively for each group. The difference was statistically significant for groups representing patients with and without diabetes. For the subgroups based on A1C values (< 5.7%, 5.7–6.4%, > 6.4%), the values of mean FVC declined with increasing A1C values (96.2%, 84.2%, 72.1%). With the division of the population in two groups, insulin sensitive and insulin resistance, based on HOMA-IR values (< 2.5 and > 2.5), mean FVC declined in the insulin resistant group compared with insulin sensitive group (98.2% compared with 74.6%). When the population was divided on the basis of LDL values into two groups (LDL > 130 mg% and LDL < 130 mg%), the mean FVC declined in the group with higher LDL values (96.2% compared with 92.7%). Duration of diabetes formed the basis of division of population in two groups (duration < 10 years and > 10 years). Mean FVC declined in the group with longer duration of diabetes (71.2% compared with 68.6%). This reduction in mean FVC values was statistically significant in all groups except those for LDL levels and duration of diabetes as shown in Tables 2 and 3 and Fig. 3.

Discussion

In this study, 52% patients with diabetes were found to have restrictive pattern on pulmonary function testing using spirometry. This was consistent with the findings of Meo et al. [5] who found that there was a combined obstructive and restrictive pattern of pulmonary function in patients with diabetes but it was predominately restrictive. The possible explanation for this includes the involvement of the neuromuscular respiratory muscles due to diabetic neuropathy of the thoracic nerves that contributes to the respiratory dysfunction. This hypothesis is strengthened by the fact that postmortem examination has revealed thickened alveolar epithelial and pulmonary capillary basal lamina in patients with diabetes which explains the deteriorated pulmonary gas exchange leading to restrictive pattern. It was also seen in the study that A1C is negatively correlated with FVC. These findings were consistent with those in the study done by Davis et al. [6]. This can be understood by the fact that A1C serves as an indicator of glycemic control over a period which can significantly correlate with the deterioration of pulmonary function in that given period of time. However, in another study done by Shah et al. [7], no significant correlation could be established between A1C and PFTs.

FVC was shown to be negatively correlated with HOMA-IR values. Similar findings were observed in studies by Lee et al. [8], Lawlor et al. [9] and Lazarus et al. [10]. This study was also able to demonstrate a significant negative correlation between FPG and lung function in the study group. Timothy [11] et al. also found similar results in their studies that higher levels of FPG were associated with lower pulmonary function. The study could not find any significant correlation between FVC and LDL values. The study also tried to correlate the effect of the duration of T2DM on the forced residual capacity. No significant correlation could be found between them. However, in the study done by Kanyakumari et al. [12], they concluded that a significant correlation exists between the duration of T2DM and reduction in FVC. In a study by Davis et al. [6], the decrease in FEV1 was at an annual rate

Table 3 : Correlation of FVC with LDL levels and duration of diabetes

LDL levels (mg%)				Duration of diabetes (years)		
Values	≤ 130	> 130	*p* value	≤ 10	> 10	*p* value
FVC	96.2	92.7	0.092	71.2	68.6	0.11

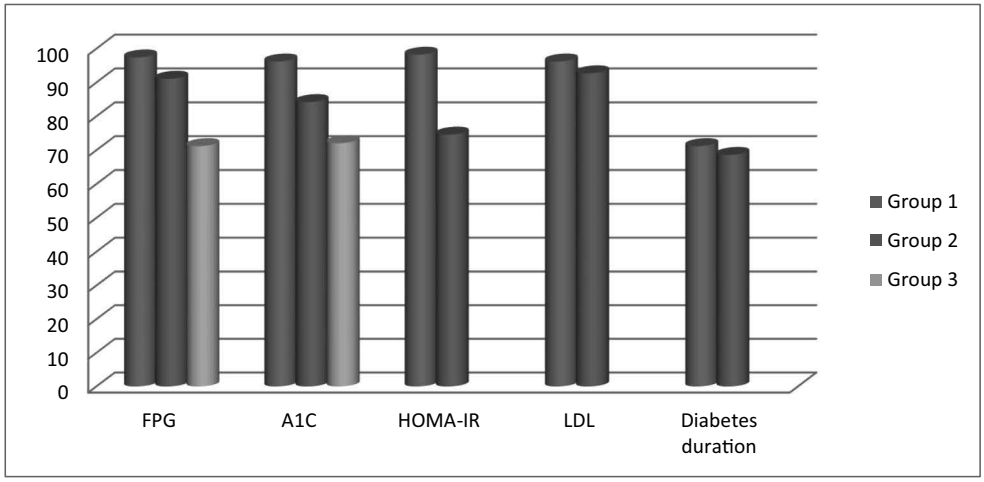

Fig. 3 Correlation of FVC with FPG, A1C, HOMA-IR, LDL and duration of diabetes

of 71 ml/year. Possible explanation can be a thickening of alveolar epithelium and pulmonary capillary basal lamina leading to pulmonary microangiopathy, reduced pulmonary elastic recoil due to nonenzymatic glycosylation of connective tissue reducing the FEV1. The major limitation was a relatively small sample size due to time-bound nature of the study. Pulmonary functions other than FEV1 and FVC were not taken into consideration. DLCO, which is a strong predictor of restrictive pattern of pulmonary disease, was not measured, due to nonavailability of facility.

Conclusion

Majority of patients (65%) had abnormal PFTs (restrictive, obstructive and mixed pattern). Restrictive pattern was predominant (52%) in patients with diabetes. Restrictive decline in pulmonary function was significantly correlated with increasing dysglycemia and insulin resistance. There was a decline in pulmonary functions with increasing duration of diabetes and extent of dyslipidemia; however, it was not significant. More studies with a higher number of patients and greater number of spirometry criteria under evaluation will be required to establish a clear cut relationship between glycemic status, insulin resistance and pulmonary function tests.

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Compliance with ethical standards

An informed consent was obtained from all included subjects after explaining them the nature and purpose of the study. All procedures performed in the study were in accordance with the ethical committee of the institution, and a prior consent for the same was obtained.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Influence of yoga on status of lipid indices in type 2 diabetes mellitus subjects

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Abstract

Background Atherogenic index of plasma (AIP) is a strong marker to predict the risk of atherosclerosis and cardiovascular disease (CVD). Diabetes alters the utilization of lipids and lipoproteins which cause diabetes-induced atherogenic dyslipidemia leading to CVD.

Objectives The study aims to determine whether yoga intervention influences lipid indices in type 2 diabetes mellitus subjects.

Methods A total of 104 persons with type 2 diabetes were included in this hospital-based prospective randomized trial. These were further randomized into non-yoga ($n = 52$) and yoga ($n = 52$) groups. Intervention of approximately 40 min yoga practice, minimum 5 times in a week over a period of 6 months, was done in the yoga group. Anthropometric parameters (body mass index (BMI) and waist-to-hip ratio (WHR)) were noted, and serum glucose (fasting and post-prandial) and lipid profile [total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL)] were estimated in all the subjects on fully automated analyzer. AIP and the logarithm of molar ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL cholesterol) were calculated. A statistical analysis was done using paired and unpaired student "*t*" test.

Results A highly significant improvement in AIP was observed in the yoga group when compared before and after yoga intervention. Body mass index also showed a similar trend. A statistically significant decrease in TC, TG, LDL, VLDL, and AIP was observed in persons with diabetes in the yoga group when compared with persons with diabetes in the non-yoga group. The result of the study suggests that 6 months of yoga intervention resulted in a significant decline in AIP in persons with type 2 diabetes ($p < 0.001$).

Conclusions Our study concluded that yoga intervention targets elevated lipid levels and aids in correcting dyslipidemia in person with diabetes.

Keywords Atherogenic index of plasma · Yoga · Type 2 diabetes mellitus

Abbreviations

BMI	body mass index
WHR	waist-to-hip ratio
TC	total cholesterol
TG	triglycerides
HDL	high-density lipoprotein
LDL	low-density lipoprotein
VLDL	very low-density lipoprotein
AIP	atherogenic index of plasma

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Background

Type 2 diabetes mellitus (T2DM) is a widespread health problem and a global threat. It has been estimated that by 2030, the prevalence of T2DM will increase by 7.7% among adults across the world thus affecting approximately 439 million people [1]. Type 2 diabetes mellitus is an endocrine disorder resulting from elevated blood glucose levels and insulin and/or decreased insulin sensitivity [2]. The enzymes and pathways involved in the lipid metabolism are affected by insulin deficiency and insulin resistance (IR) in diabetes mellitus.

There is a 2–4 times higher risk of cardiovascular (CV) mortality in patients with type 2 diabetes mellitus as compared to persons with no diabetes [3]. Alterations in lipid and lipoprotein profile contribute to atherosclerosis in T2DM [4]. Dyslipidemia is an established risk factor for cardiovascular

disease (CVD), which is assessed by estimating the levels of plasma lipid and lipoprotein. Lipid ratios are better predictors of coronary artery diseases as compared to lipids alone and strongly indicate an atherogenic risk. As the sub-fractionation of lipoproteins cannot be undertaken in all the clinical laboratories, a correlation exists between the atherogenic index of plasma (AIP), size, and composition of lipoproteins [5]. The AIP is a mathematical relationship between triglycerides (TG) and high-density lipoprotein cholesterol (HDL-c) which is an index for assessing factors of CV risk [6]. The ratio depicting the association of TGs and HDL-C shows the equilibrium between risk and protective lipoprotein forces. AIP values associated with a low, intermediate, and increased risk of CVD are 0.11, 0.11 to 0.21, and more than 0.21, respectively [7]. AIP has been used to quantify blood lipid levels and commonly used as an optimal indicator of dyslipidemia and associated diseases (e.g., CVD). Assessment of cardiovascular risk factors to predict acute coronary events can be done by AIP which is an index of the highest sensitivity and has a predictive role for atherosclerosis.

Heterogeneity of LDL-C particles and the atherogenicity of lipids and lipoproteins other than LDL-C have been an area of research over the past decade based on this; atherogenic dyslipidemia, defined as high LDL-C/ HDL-C ratio and high TAG, is associated with high cardiovascular risk. For better evaluation and to predict the risk of CVD, many clinical studies have attempted to introduce another marker of atherogenic dyslipidemia such as atherogenic index (AI) and coronary risk index (CRI).

Treatment and management of T2DM focus on lifestyle changes such as diet, enhanced activity, and properly self-managing symptoms and prescribed treatments. Evidence-based clinical studies have recommended training exercises as a cardinal non-pharmacotherapy [8]. The role of yoga asanas and pranayama has been studied in various chronic diseases, such as hypertension, asthma, chronic obstructive pulmonary disease, and diabetes [9].

Yoga practice has health benefits and results in physically fit, relaxed, and overall well-being of an individual. The principle of yoga is based on the close relationship of the mind and body. Yoga is an inexpensive regimen to maintain that is an efficacious, safe, and cost-effective method. Yoga asanas and pranayama practice aids in controlling of T2DM and can serve as an adjunct to medical therapy [10]. Diabetes is a lifestyle disorder that has a scope of lifestyle intervention and can provide relief from rising costs for drugs and investigations and financial burden unaffordable by the majority of the community in India. Studies are scarce on the interrelationship between dyslipidemia, AIP, and T2DM especially in Asians.

Since dyslipidemia is considered as a strong indicator to predict CV risk, the study was undertaken to assess the effect of yoga on lipid indices and correlation between AIP, BMI, TG, and HDL cholesterol in subjects with T2DM.

Methods

Study population

This was a hospital-based prospective randomized trial of yoga intervention that was conducted in the Department of Biochemistry, RUHS College of Medical Sciences and Associated Hospital, Jaipur. A total of 127 T2DM subjects of either gender were approached and screened. Out of which, 115 subjects gave consent. Further, out of 11 subjects, 8 subjects of the yoga group did not adhere to the intervention protocol and 3 subjects of the yoga group were not available for follow-up. The age group of subjects was between 30 and 65 years. The subjects were divided into two groups viz. non-yoga ($n = 52$) and yoga ($n = 52$) groups. Intervention of approximately 40 min yoga practice, minimum of 5 times in a week over a period of 6 months, was done in the yoga group. Subjects of both groups continued their conventional medicines of oral hypoglycemic agents. The dose of these medicines remained constant throughout the study period. Statins were not prescribed to the subjects enrolled in the study.

The integrated approach to yoga therapy included prayer, Omkar recitation, yoga posture (asanas), and breathing (pranayam). All training sessions were conducted under the supervision of a certified professional yoga instructor.

Schedule of yoga

	Rounds	Approximate duration (s)	
Prayer	Omkar 3 times	60	
Trikonasana	6	60	
Katichakrasana	6	60	
Surya Namaskaras	9	90 s each	
Arthamatsyendrasana	Each side 90 s × 2	180 × 2	
Pavanamuktasana	4	90 s each	
Bhujangasana	2	90 × 2	
Dhanurasana	2	90 × 2	
Padachakrasana	Clock/anti-clock 15 + 15	120	
Pranayamas	i) Rechaka, Puraka	20 units*	60
	ii) Bhastrika	5 units**	60
	iii) Nadi Shodhana	1–24 × 2	90
Prashantha asana/meditation	–	10 mins	

*1 Inhale, 1 Exhale = 1 unit; **4 expulsions, 1 long breath = 1 unit

The subject relaxed at the end of the yoga session with 10 min of prashantha asana followed by meditation practice for relaxation.

The diagnosis of diabetes was done as per the American Diabetes Association (ADA)/European Association of Study

of diabetes criteria (EASD) (fasting blood glucose (FBS) ≥ 126 mg/dl and post-prandial blood glucose ≥ 200 mg/dl, HbA1c ≥ 6.5) [11].

Subjects with history of acute and chronic infections, connective tissue disease, viral infections in the last 1 year, myalgia, myositis, myopathy, cancer, pulmonary tuberculosis, hemolytic disease, chronic obstructive pulmonary disease (COPD), bronchial asthma, rheumatoid arthritis, thyroid disorders, and subjects who were seriously ill and unable to give informed consent were excluded.

Ethical clearance for the study was taken from the institutional ethics committee prior to the study. The purpose and nature of the study were explained to all eligible subjects. A written informed consent and a detailed physical and clinical examination were conducted at baseline and after 6 months. A detailed history of the subjects including age, gender, and disease history with details of treatment viz. drug, their dosage, and duration was noted.

Anthropometric and physical measurements

Standard protocols with participants wearing light clothing without shoes were used to measure body weight using a weighing machine (Contech, CP-150k10, India) and height by using a stadiometer (Standard steel, ch01, India). Body mass index (BMI) was calculated. Waist and hip circumferences were measured using metal tape. All subjects were introduced to standard lifestyle measures.

Sample collection and biochemical analysis

After fasting for 10–12 h, venous blood samples were withdrawn under aseptic conditions and collected into plain and EDTA-coated vacutainers. Serum glucose (fasting and post-prandial) and lipid profile were estimated in all the subjects on a fully automated analyzer at baseline, and a repeat of baseline tests was conducted at the end of 6 months. Serum glucose (GOD-PAP end point method) [12], TG (GPO-PAP method) [13], TC (COD-PAP method) [14], and HDL-c (enzymatic direct HDL method) [15] were estimated by enzymatic method. The Friedewald equation was used to calculate the low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [16]. AIP, the logarithm of molar ratio of TG to high-density lipoprotein cholesterol (TG/HDL cholesterol), was calculated [17].

Statistical analysis

The groups' mean ± SD was calculated for each study variable and significant difference between means evaluated using the paired and unpaired student "*t*" test. Pearson correlation analysis was performed to study the association between parameters. Statistical Package for Social Science (SPSS) version 22.0 software for windows was used, with $p < 0.05$ considered as statistically significant.

Results

The distribution of type 2 diabetes mellitus subjects according to age and gender is shown in Table 1. Out of 104 of type 2 diabetes mellitus subjects, 57 (55%) were male and 47 (45%) were female. In the non-yoga group, 25 were male and 27 were female, and in the yoga group, 32 were male and 20 were female. The average duration of diabetes in the recruited subjects was 2 to 8 years.

A highly significant decrease in BMI and waist-to-hip ratio was observed in the yoga group after 6 months of yoga therapy as compared to the non-yoga group. Six months of yoga therapy resulted in a highly significant decrease in both fasting and post-prandial serum glucose in type 2 diabetics. After the comparison of the lipid profile of the non-yoga and yoga groups at baseline, there was a significant decrease in TC, TG, VLDL, and AIP and highly significant in LDL between the groups. A decrease in the levels of serum TC, TG, and LDL observed which was found to be statistically significant and a significant decrease in VLDL were observed in the yoga group after 6 months of yoga therapy as compared to the non-yoga group. A highly significant increase in HDL cholesterol levels was observed in the T2DM yoga group after 6 months of yoga therapy when compared with the non-yoga group (Table 2).

AIP for persons with type 2 diabetes in the yoga group was 0.23 ± 0.19 at baseline and 0.06 ± 0.17 after 6 months of yoga therapy. A significant decrease in AIP was observed in the yoga group after 6 months of yoga intervention ($p < 0.001$).

Correlation between AIP and various anthropometry and biochemical parameters was analyzed in the yoga group after 6 months of yoga therapy. The Pearson correlations between AIP and TG, AIP and HDL, AIP and BMI, and HDL and BMI are shown in Fig. 1. The correlation analysis found a highly significant negative correlation of AIP with HDL and HDL with BMI, and there was a highly significant positive

Table 1 The distribution of type 2 diabetes mellitus subjects according to age and gender

Age (years)	Non-yoga group ($n = 52$)		Yoga group ($n = 52$)	
	Male	Female	Male	Female
30–40	2 (8%)	1 (4%)	2 (6.25%)	1 (5%)
40–50	8 (32%)	11 (41%)	12 (37.5%)	2 (10%)
50–60	11 (44%)	14 (51%)	11 (34.37%)	15 (75%)
60–70	4 (16%)	1 (4%)	7 (21.87%)	2 (10%)
Total	25	27	32	20

Table 2 Comparison of anthropometry and biochemical parameters in the non-yoga and yoga groups at baseline and after 6 months of yoga therapy

Parameters	Non yoga ($n = 52$)			Yoga ($n = 52$)		
	Baseline	After 6 months	p value	Baseline	After 6 months	p value
BMI (kg/m^2)	28.15 ± 3	28.02 ± 3	0.515	28.14 ± 3	25.11 ± 3	0.000**
WHR	0.99 ± 0.06	0.98 ± 0.05	0.876	0.99 ± 0.06	0.92 ± 0.06	0.000**
Blood sugar (F) (mg/dL)	164 ± 47	156 ± 45	0.221	183 ± 53	130 ± 36	0.000**
Blood sugar (PP) (mg/dL)	253 ± 65	225 ± 65	0.061	234 ± 62	174 ± 66	0.000**
TC (mg/dL)	188 ± 50	183 ± 48	0.375	209 ± 42	153 ± 33	0.000**
TGs (mg/dL)	151 ± 76	147 ± 53	0.484	182 ± 55	125 ± 32	0.000**
HDL (mg/dL)	45 ± 14	40 ± 7	0.036*	46 ± 21	50 ± 12	0.274
LDL (mg/dL)	147 ± 54	172 ± 51	0.001**	200 ± 44	127 ± 34	0.000**
VLDL (mg/dL)	30 ± 15	29 ± 11	0.484	36 ± 11	24 ± 6	0.001**
AIP	0.12 ± 0.28	0.18 ± 0.17	0.065	0.23 ± 0.19	0.06 ± 0.17	0.000**

*Significant at $p < 0.05$

**Highly significant at $p < 0.001$

correlation of AIP with TG and AIP with BMI (Fig. 1a–d). Regression equation of AIP with TG is AIP = 0.0036 × TG − 0.4211. Regression equation of AIP with HDL is AIP = 0.5616–0.0099 × HDL. Regression equation of AIP with BMI is AIP = 0.03733 × BMI = 0.812. Regression equation of BMI with HDL is BMI = 31.253–0.153 × HDL.

Discussion

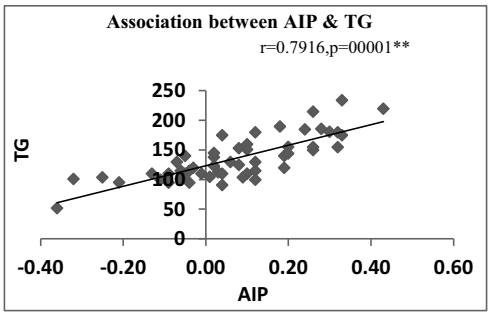
Both multiple metabolic and vascular abnormalities in type 2 diabetes mellitus, such as dyslipidemia, endothelial dysfunction, insulin resistance, and vascular inflammation, individually represent as the major risk factors for the CVD [18]. In the present study, in both the study groups, TC, TG, LDL, and AIP were found to be higher than normal values in persons with type 2 diabetes at baseline. Lipid ratios and AIP have been reported to indicate atherogenic dyslipidemia. Similar findings were reported by Suchitra et al. in their study to assess atherogenic dyslipidemia in T2DM and diabetic nephropathy patients [19]. Nimmanapalli et al. [20] reported a significant difference in total cholesterol, TG and HDL, VLDL, LDL, lipid ratios, and atherogenic indices (AC and AIP) when compared between patients and control groups.

Persons with diabetes frequently have risk factors for atherosclerosis among which dyslipidemia is likely to play a major role in the excess CVD mortality associated with the conditions [21]. Quality of life is adversely affected by diabetes which is a chronic metabolic disease. Exercise is an important therapeutic modality that involves the treatment of diabetes mellitus [22]. The various postures performed during yoga practice aid in improving the sensitivity of β cells to glucose; this results in improved secretion and increase the blood supply to the muscle and muscle relaxation, thus improve uptake of glucose. Proinflammatory responses are reduced and improved by yoga therapy resulting in immunomodulation [23].

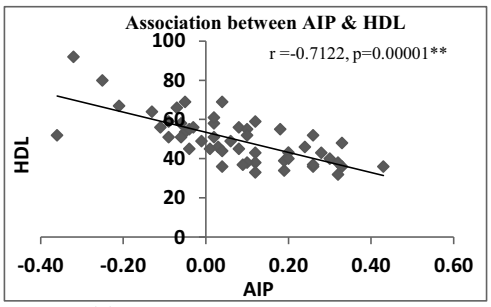
In our study, a significant improvement in lipid profile in persons with type 2 diabetes performing yoga therapy was observed. There was a highly significant reduction in serum total cholesterol, TG, and LDL cholesterol concentration in the yoga group when compared with the non-yoga group after 6 months. A similar trend was observed when intragroup comparison was done in the yoga group at baseline and 6 months of yoga therapy. Our results are in accordance with the previous study which reported that HDL levels were raised and very low-density lipoprotein cholesterol and TG were decreased by physical activity [24]. The increase in HDL-c was, however, not found to be significant in our study. Practice of yoga *asana* modulate gene expression; improves strength, endurance, flexibility, and balance; and increase muscle activity that results in favorable effects on body weight, adiposity, dyslipidemia, and insulin resistance [25].

A decrease in body weight and BMI was observed in the yoga group after the intervention of yoga therapy for 6 months when compared with baseline values and with the non-yoga group also. In the previous study, a significant increase in AI linked with an increase in BMI ($p < .05$) has been reported in middle-aged women [24].

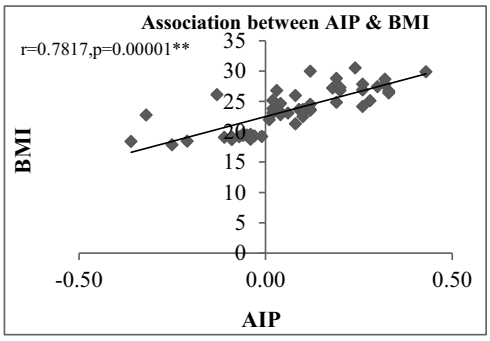
AIP in persons with diabetes of the yoga group was observed to be significantly decreased when compared with AIP at baseline before the intervention of yoga therapy. In our study, AIP in the non-yoga group is higher as compared to the yoga group. It has been reported that AIP is a better predictor of CAD as compared to TG or HDL. The use of TG and HDL simultaneously to calculate AIP is beneficial in predicting plasma atherogenicity. TG and HDL ratio is a



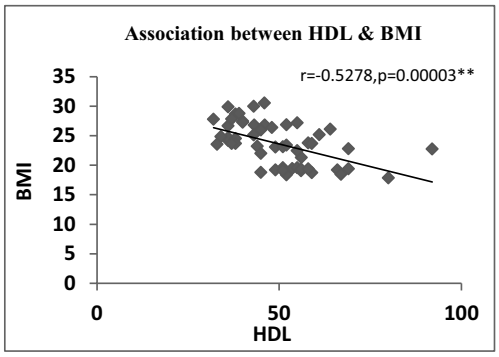
(a) Scatter plot between AIP and TG



(b) Scatter plot between AIP and HDL



(c) Scatter plot between AIP and BMI



(d) Scatter plot between HDL and BMI

Fig. 1 The correlation of the atherogenic index of plasma with body mass index (**c**), triglycerides (**a**), high-density lipoprotein (**b**), and correlation of HDL with BMI (**d**) in the yoga group after 6 months of yoga therapy. *Significant at $p < 0.05$. **Highly significant at $p < 0.001$

strong predictor of myocardial infarction [26].AIP can be used as an alternative screening tool in situations where all atherogenic parameters are normal.

Dyslipidemia is a major cause of morbidity and mortality in persons with type 2 diabetes. The most common pattern is observed in triglyceride and LDL and decreased HDL cholesterol concentrations [27]. Data has suggested that LDL is more atherogenic as modifications of LDL lipoprotein increase atherogenicity in T2DM [28]. The alteration in the serum lipid profile, that is, an increase in TC, TG, and LDL-C, and decrease in HDL-C are major factors contributing to the development of CVDs.

Innes et al. [29] suggested that yoga may help in improving core problems of the metabolic syndrome like hyperglycemia and insulin resistance, deranged lipid profiles, and anthropometric characteristics. The present study confirmed the positive effects of yoga therapy on blood sugar levels and lipid indices in person with type 2 diabetes over 6 months. The result of the study points to benefit persons with diabetes with relation to the risk associated with dysfunction of lipid metabolism.

Information regarding atherogenicity of plasma provided by AIP, quantifies the response to therapeutic intervention and inversely correlates with insulin sensitivity measurement [30]. These findings suggest the effects of yoga therapy on lipid ratios which identify the CV risk rather than their individual lipids alone. The present study has shown significant positive correlation of AIP with TG and AIP with BMI. AIP has significant negative correlation with HDL. HDL has significant negative correlation with BMI.

Conclusion

It is crucial to identify and address the CVD risk in persons with diabetes at an early age. AIP and lipid ratios are useful indicators of cardiovascular risk. The findings of the study suggest that yoga therapy has a therapeutic and protective effect in type 2 diabetes by improving lipid indices.

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Authors' contributions SS was responsible for the study conception, design, and guidance to the research. SB and BG drafted the manuscript. SB performed the acquisition of the data. SB and SJ conducted the data and sample collection. SB, SJ, and BG performed the statistical analysis and interpretation of the data. SS critically reviewed the manuscript. SS gave administrative, technical, and material support. All authors contributed to and approved the final version of the manuscript.

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Data availability Data from this project will not be shared because additional results from the study are yet to be published.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethics approval and consent to participate This study was approved by the Ethical Committee of the RUHS-CMS, Jaipur, Rajasthan, India (Registration No. ECR/762/Inst/RJ/2015). All participants signed an informed consent prior to their participation.

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ORIGINAL ARTICLE

ABCD score of > 6 predicts diabetes remission following bariatric surgery

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Abstract

Introduction Bariatric surgery is recommended as a treatment option in individuals with T2DM and BMI > 35 kg/m^2. However, remission of diabetes following bariatric surgery has varied from 24–73% in various studies. A number of scoring systems have been proposed to predict remission of type 2 diabetes mellitus following bariatric surgery. Out of these ABCD score has shown the most promise. The aims of this study were to analyze the effects of bariatric surgery on T2DM patients and to evaluate the possibility of using ABCD score to help with the patient selection.

Material and methods Between 1 January 2016 and 1 December 2017, patients undergoing bariatric surgery for obesity with T2DM were recruited from DMCH Ludhiana and followed up at 3 months and 6 months after surgery for control/remission of diabetes.

Results At 6 months, the mean % EWL was 62.74. Significant improvements were noted in FBS (193.05 to 107.97), in HbA1C (8.22 to 6.17), dose of OHAs (1.97 to none), and insulin (32.86 to 5.66). Patients who attained remission were younger, with shorter duration of diabetes and higher C-peptide levels. The preoperative BMI or the % EWL were not predictive of diabetes remission. Higher ABCD scores were significantly associated with higher rates of diabetes remission.

Conclusion Bariatric surgery leads to substantial weight loss and amelioration of type 2 diabetes. An ABCD score of > 6 predicts diabetes remission following bariatric surgery, and is recommended as an aid for patient selection and counseling.

Keywords Diabetes · Obesity · Bariatric surgery · Remission · ABCD score

Introduction

In 2013, 2.1 billion people worldwide were overweight, out of which 671 million people were categorized as obese [1]. The World Health Organization (WHO) defines obesity as a condition of excessive fat accumulation in the body to the extent that health and well-being are adversely affected.

Fontaine et al. estimated that a severely obese (BMI > 45) male at age 20 would live 13 years less and a female 8 years less than a nonobese individual [2]. Besides, obesity is associated with numerous comorbidities – type 2 diabetes mellitus/dysglycemia, dyslipidemia, hypertension, arthritis/degenerative joint disease, sleep apnea, asthma, and gastroesophageal reflux. Obese individuals also face social discrimination and discrimination in employment.

Bariatric surgery has been associated with improvement or near resolution of T2DM in obese patients. The American Diabetes Association clinical guidelines recommend bariatric surgery as a treatment option in individuals with diabetes mellitus and a body mass index > 35 kg/ m^2 [3]. Numerous studies have shown that bariatric surgery is superior to conventional medical treatment in achieving remission of T2DM in obese individuals. However, the resolution of T2DM following metabolic surgery is not universal ranging from 24–73% in various studies.

Several clinical and biochemical factors proposed as predictors of T2DM resolution after weight loss surgery are age, BMI, duration of T2DM, the severity of T2DM, fasting blood glucose, glycosylated hemoglobin (HbA1C), and C-peptide level. Several scoring systems have also been developed to predict T2DM remission following bariatric surgery [4]. Of these, the ABCD score has shown the most promise.

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The ABCD diabetes surgery score was proposed by Lee et al. in their paper published in 2012 [5]. The ABCD diabetes surgery score consists of four variables of independent predictors of T2DM remission: patient age, BMI, C-peptide level, and duration of diabetes (Table 1). This study was conducted to evaluate the possibility of using the ABCD score to help with patient selection.

Materials and methods

Between 1 January 2016 and 1 December 2017, patients undergoing bariatric surgery for obesity with T2DM were recruited from DMCH Ludhiana and followed up at 3 months and 6 months after surgery.

The study was approved by the Research & Ethical Committee DMCH, and all participants gave signed informed consent. The inclusion criteria were BMI > 35 kg/ m^2 with type 2 diabetes mellitus, aged 18–67 years, having undergone 6 months of medical treatment, having an acceptable operative risk, and highly motivated patients for bariatric surgery. The exclusion criteria were any previous bariatric surgery, obesity related to endocrinological disorders, e.g., Cushing syndrome, other familial syndromes, etc., diabetes mellitus type 1 (C-peptide level < 0.9 ng/mL).

Preoperatively, anthropometric measurements – height, weight, BMI, and laboratory tests – plasma C-peptide, fasting blood sugar (FBS), and glycosylated hemoglobin (HbA1C) were done. On follow-up at 3 months and 6 months after surgery, the following parameters were recorded – FBS, HbA1C, weight, and BMI. The dose of oral hypoglycemic agents (OHAs) and/or insulin being taken by the patient was also noted.

Complete remission of T2DM was defined as an HbA1C value < 6% without the use of oral hypoglycemics or insulin, and partial remission was defined as HbA1C value < 6.5% [7]. Patients with HbA1C < 7% after surgery were considered to be improved. The remission rate was evaluated using the ABCD score.

Operative technique

The surgical techniques used were standard laparoscopic bariatric surgery (Roux-en-Y gastric bypass, mini gastric bypass, sleeve gastrectomy).

Table 1 ABCD score [6]

Variable	Points on the ABCD index			
	0	1	2	3
Age (year)	≥ 40	≤ 40		
BMI (kg/m^2)	< 27	27–34.9	35–41.9	≥ 42
C peptide (mmol/L)	< 2	2–2.9	3–4.9	≥ 5
Duration (year)	> 8	4–8	1–3.9	< 1

Table 2 Number of patients according to ABCD score (total 60)

	0	1	2	3
Age (year)	≥ 40(43)	≤ 40(17)		
BMI (kg/m^2)	< 27(0)	27–34.9(0)	35–41.9(22)	≥ 42(38)
C peptide (mmol/L)	< 2(5)	2–2.9(7)	3–4.9(24)	≥ 5(24)
Duration (year)	> 8(5)	4–8(18)	1–3.9(28)	< 1(9)

Statistical methods

The obtained data is presented as a mean ± standard deviation, ranges, numbers, and percentage according to the requirement. The results were analyzed using paired t-test and chi-square test ($\chi 2$ test). The statistical analysis was conducted using the SPSS (version 17) for Windows statistical package. The $p < 0.05$ was considered statistically significant.

Results

Sixty patients underwent bariatric surgery (Table 2), out of which 29 underwent LMGB, 27 underwent LSG, and 4 underwent LRYGB. The mean age was 47.3 ± 11.53, mean preoperative BMI was 45.24 ± 7.26, mean C peptide was 4.86 ± 2.30, and mean duration of diabetes was 3.75 ± 3.44.

There occurred significant improvement in FBS from 193.05 preoperatively to 136.95 at 3 months and 107.97 at 6 months, in HbA1C from 8.22 preoperatively to 7.01 at 3 months and 6.17 at 6 months, and in BMI from 45.24 preoperatively to 36.26 at 3 months and 32.56 at 6 months (Table 3). The dose of OHAs and insulin was also reduced significantly.

In our study, 44.44% EWL occurred at 3 months, and 62.74% EWL occurred at 6 months.

At 6 months, 33 patients (55%) achieved complete remission of diabetes, 11 patients (18.3%) had partial remission of diabetes, 8 patients (13.3%) had significant improvement in their diabetic status, while 8 patients (13.3%) either failed to improve or had non-significant improvement in their diabetic status (Fig. 1).

Higher C-peptide levels were associated with higher rate of diabetes remission with 68.1% of patients with elevated C-peptide levels (> 3.2 ng/ml) achieving diabetes remission vs 7.7% of patients with a normal C-peptide level (0.5–3.2 ng/ml).

Higher ABCD scores were significantly associated with higher rates of diabetes remission with no remission occurring in patients with ABCD score ≤ 4, and 100% remission occurring in patients with ABCD score ≥ 9 (Table 4).

Patients on OHAs alone preoperatively had a much higher remission rate at 6 months after surgery (75.8%) as compared to patients using insulin with/without OHAs (24.2%).

Table 3 Comparison of characteristics preoperatively and postoperatively

	Pre-op Mean ± SD	Post-op (at 6 months) Mean ± SD	Difference Mean ± SD	*T*	*P* value
FBS (mg/dl)	193.05 ± 43.04	107.97 ± 25.19	85.083 ± 28.924	22.786	0.000
HbA1C (%)	8.22 ± 1.30	6.17 ± 0.90	2.052 ± 0.657	24.197	0.000
Insulin requirement (U)	32.86 ± 12.44	5.66 ± 9.70	27.21 ± 1.82	14.913	0.000
OHA requirement (n)	1.97 ± 1.30	0.00 ± 0.00	1.97 ± 1.30	2.747	0.010
Weight (kg)	121.57 ± 22.74	87.70 ± 15.40	33.87 ± 13.64	19.240	0.000
BMI (kg/m^2)	45.24 ± 7.26	32.56 ± 4.27	12.67 ± 5.25	18.685	0.000

Patients undergoing diabetes remission had significantly lower preoperative FBS and HbA1C levels, shorter duration of diabetes, higher C-peptide levels, higher ABCD scores, and lower preoperative insulin and OHA use. The preoperative weight or BMI was not significantly different among remission and the non-remission groups (Table 5).

The % EWL for the remission and non-remission group was 43.22 ± 10.04 and 45.84 ± 12.05, respectively at 3 months, and 62.62 ± 13.06 and 62.88 ± 14.44 respectively at 6 months which was not significantly different.

The mean decrease in FBS at 3 months and 6 months was greatest for LSG at 64.30 and 94.07 mg/dl, while the mean reduction in FBS for LMGB and LRYGB at 3 months and 6 months was similar at 49.03 and 76.90 and 52.00 and 83.75 mg/dl, respectively. The mean decrease in HbA1C at 3 months and 6 months was highest for LSG at 1.26 and 2.17, while the mean reduction in HbA1C for LMGB and LRYGB at 3 months and 6 months was similar at 1.18 and 1.96 and 1.15 and 1.93, respectively.

The % EWL at 3 months and 6 months was similar in the case of LRYGB and LMGB at 57.10 and 72.81 and 49.30 and 72.60, respectively, while it was lower in the case of LSG at 37.35 and 50.66.

The ABCD score of 6 provided the best balance of sensitivity and specificity for predicting diabetes resolution at 6 months. The % remission was 24% for the ABCD score ≤ 6 and 77.14% for ABCD score > 6.

Discussion

We analyzed the effects of bariatric surgery on type 2 diabetic patients and explored the possibility of using the ABCD score as an aid in patient selection.

The preoperative C-peptide levels were above normal in 78.3% of our patients and normal in 21.7% of patients, a finding consistent with the results reported by Deep et al. [8], reflecting the hyperinsulinemia associated with type 2

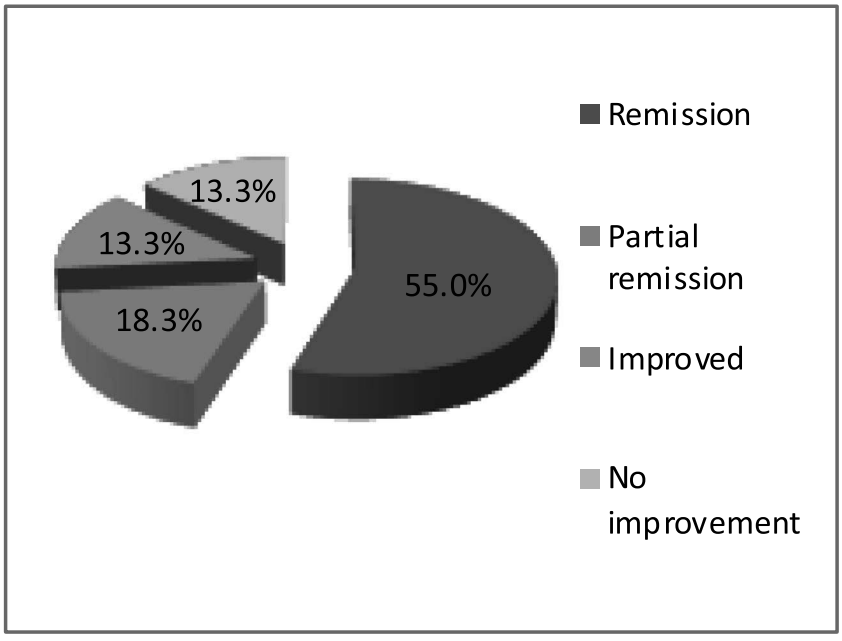

Fig. 1 Status of diabetes at 6 months

Table 4 Status of diabetes at 6 months according to ABCD scores

ABCD Score	Total					% of complete remission	Chi square value	*P* - value
		No improvement	Improved	Partial improvement	Remission			
3	2	2	0	0	0	0.0%	63.991	0.000
4	4	2	2	0	0	0.0%		
5	7	4	2	0	1	14.3%		
6	12	0	4	3	5	41.7%		
7	15	0	0	6	9	60.0%		
8	12	0	0	2	10	83.3%		
9	7	0	0	0	7	100.0%		
10	1	0	0	0	1	100.0%		
Total	60	8	8	11	33	55.0%		

diabetes. The diabetes remission rate was significantly higher in patients with C-peptide levels > 3.2 ng/ml (68.1%) than patients with C-peptide levels < 3.2 ng/ml (7.7%) which was consistent with studies by Lee et al. [9] and Dixon et al. [10].

There occurred significant weight loss following bariatric surgery with a mean weight loss of 44.44% EWL at 3 months and 62.74% EWL at 6 months which was consistent with the findings of the systemic review by Gloy et al. [11] The % EWL at 3 months and 6 months was similar in the case of LRYGB and LMGB at 57.10 and 72.81 and 49.30 and 72.60, respectively, while it was lower in the case of LSG at 37.35 and 50.66 which was consistent with the findings reported in the systemic review by Chang et al. [12]

Significant improvement was also noted in FBS from 193.05 preoperatively to 136.95 at 3 months (Difference 56.10 ± 19.20) and 107.97 at 6 months (Difference 85.08 ± 28.92), and in HbA1C from 8.22 preoperatively to 7.01 at 3 months (Difference 1.21 ± 0.37) and 6.17 at 6 months (Difference 2.05 ± 0.66) which was in line with the FBS and HbA1C reduction reported in the systemic review by Ribaric et al. [13]

The dose of OHAs (1.97 ± 1.30 preop to 0.29 ± 0.59 at 3 months and none at 6 months) and insulin (32.86 ± 12.44 preop to 16.79 ± 11.72 at 3 months and 5.66 ± 9.70 at 6 months) was also reduced significantly which was consistent with the results reported by Schauer et al. [14], Ikramuddin et al. [15], and Dorman et al. [16].

Fifty five percent of patients in our study had complete remission of diabetes at 6 months which was slightly lower than the overall diabetes remission rate reported in the meta-analysis by Ribaric et al. [13] (63.5%) at a median follow-up of 18 months.

Patients who attained remission were younger (44.03 ± 11.18 vs 51.44 ± 10.79), had a shorter duration of diabetes (2.60 ± 2.32 vs 5.17 ± 4.05), higher C-peptide levels (5.94 ± 2.04 vs 3.55 ± 1.91), higher ABCD scores (7.61 ± 1.17 vs 5.63 ± 1.39), lower preoperative FBS (167.79 ± 16.89 vs 223.93 ± 45.30) and HbA1C levels (7.42 ± 0.51 vs 9.19 ± 1.30), and lower preoperative insulin (15.70 ± 12.29 vs 37.90 ± 9.09) and OHA requirement (1.56 ± 1.00 vs 3.67 ± 1.03). This was consistent with the results of the meta-analysis by Wang et al. [17] Older age, longer duration of diabetes and lower C-

Table 5 Comparison of preoperative characteristics between remission and non-remission groups

	Remission mean ± SD	Non-remission mean ± SD	*T*	*P* value
Age	44.03 ± 11.18	51.44 ± 10.79	2.596	0.012
Height	1.64 ± 0.11	1.63 ± 0.09	−0.325	0.747
Weight	121.73 ± 24.45	121.37 ± 20.93	−0.060	0.952
BMI	45.08 ± 7.63	45.43 ± 6.91	0.186	0.853
C peptide	5.94 ± 2.04	3.55 ± 1.91	−4.651	0.000
Duration of D.M.	2.60 ± 2.32	5.17 ± 4.05	3.082	0.003
FBS(preop)	167.79 ± 16.89	223.93 ± 45.30	6.590	0.000
HbA1C(preop)	7.42 ± 0.51	9.19 ± 1.30	7.163	0.000
Insulin(preop)	15.70 ± 12.29	37.90 ± 9.09	5.671	0.000
OHA (preop)	1.56 ± 1.00	3.67 ± 1.03	4.595	0.000

peptide levels reflect lower β-cell reserve and are associated with lower chances of diabetes remission after surgery. Poorer glycemic control and higher medication use preoperatively are associated with increased disease severity, and such patients are less likely to benefit from surgery.

In our study, preoperative weight, BMI, or % EWL was not predictive of diabetes remission which was in line with the findings of Mingrone et al. [18] and Panunzi et al. [19] However other studies by Raj et al. [20], Dixon et al. [21], Lee et al. [22], and Bhasker et al. [23] have found higher preoperative weight and BMI to be predictive of diabetes remission after bariatric surgery.

Higher ABCD scores were significantly associated with higher rates of diabetes remission with no remission occurring in patients with ABCD score ≤ 4, and 100% remission occurring in patients with ABCD score ≥ 9 which was consistent with the results reported by Lee et al. [5, 6, 24] and Raj et al. [20]

Patients on OHAs alone preoperatively had a much higher remission rate at 6 months after surgery (80.6%) as compared to patients using insulin with/without OHAs (27.5%) which was statistically significant.

The mean decrease in FBS and HbA1C was higher after LSG than LMGB and LRYGB though it was not statistically significant. There is lack of consensus in the literature regarding the type of surgery offering the best outcome for diabetes with some studies reporting higher remission rates after gastric bypass [25–27], some reporting higher remission following sleeve gastrectomy [28] and others finding no significant difference in the remission rate [29–32].

The receiver operating characteristic (ROC) analysis showed area under the curve of 0.858 with ABCD score of > 6 providing the best balance of sensitivity and specificity for predicting diabetes resolution at 6 months. For patients with an ABCD score ≤ 6, diabetes remission occurred in 24% of patients at 6 months while for patients with an ABCD score > 6, diabetes remission occurred in 77.1% of patients.

Our study had some limitations. The total number of patients in our study was relatively small. The follow-up period after surgery of 6 months was short. Our study was conducted at a single institution. Further studies with a larger number of patients at multiple centers with ethnically diverse populations and a longer follow-up are needed.

Conclusion

Bariatric surgery leads to substantial weight loss and amelioration of type 2 diabetes. ABCD score of > 6 provides the best sensitivity and specificity for predicting diabetes remission after surgery and is recommended as an aid for patient selection and counseling.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate The study was approved by the institutional ethics committee.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Research & Ethical Committee, DMCH, Ludhiana – ECR/101/Inst/PB/2013/RR-16) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Consent Informed consent was obtained from all individual participants included in the study.

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ORIGINAL ARTICLE

Secular trends and rural-urban differences in endocrine and metabolic disease mortality in China: an age-period-cohort modeling of National Data

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Abstract

Objectives Annual mortality of endocrine and metabolic diseases (EMD) in a population reflects levels of economy-related lifestyles and medical care, both of which have changed substantially in China in the last hundred years. Linking these two factors with historical trends of EMD will enhance our understanding of the EMD epidemiology.

Methods Age-specific annual mortality rates of EMD from 1991 to 2016 were derived from the Health Statistics Yearbook of China and analyzed by rural and urban using age-period-cohort (APC) method. Intrinsic estimator was performed for parameter estimation.

Results The data fit APC models well. After controlling the influence of age, the estimated period effect increased rapidly from 1991 to 2001 before it leveled off. The risk for urban area increased faster than for rural area before 2006. Contrarily, the estimated cohort effects across 100 years from 1911 to 2016 showed an overall declining trend. For urban area, the cohort effect declined progressively since the 1911–1915 birth cohort with small fluctuations, while the same effect for rural area increased slowly from the 1911–1915 cohort to the 1951–1956 cohort before it declined, intercepting twice with that of urban one at cohort 1941–45 and another at 1996–2000.

Conclusion Increases in EMD mortality in China since 1991 can be explained primarily by the period effect, reflecting unhealthy lifestyles adapted along with rapid economic growth. The 100-year declines in cohort effect and the rural-urban differences could be largely attributed to the overall progress and rural-urban inequity in medical and healthcare. Future public health planning and decision-making must emphasize these two factors.

Keywords Endocrinology and metabolism · Annual mortality · APC model · Lifestyle change · Urban-rural China

Introduction

Endocrine and metabolic diseases (EMD) are used as a general term to include a series of diseases that are related to the endocrine system, and all EMD has one character in common: metabolic disorders. To a great extent, EMD can be considered as the most common causes for neuropathy [1]. According to International Classification of Diseases-10, EMD include diabetes, thyroid diseases, adrenal gland disorders, etc. [2]. Among these diseases, diabetes accounts for the most and is nutritionally and metabolically the most pervasive [3]. Except for the risk of death, EMD are associated with many complications, such as kidney [4], brain, and heart [5] disease. Consequently, EMD may increase the risk of death from other diseases and reduce the life expectancy of a population [6]. EMD has become a major public health concern in China and across the globe. Data from Chinese statistics indicate a rapid increase in the number of persons died from EMD. In urban area, the annual mortality of EMD increased from 10.11 per 100,000 in 1990 to 20.43 per 100,000 in 2016.

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During the same period, there was a threefold increase in the rural [7].

Economic growth is often associated with increasing EMD annual mortality. China is one of the fastest growing countries in the world. Along with rapid economic growth, urbanization, and globalization, lifestyle is shifting rapidly from a traditional agricultural lifestyle toward a modern luxury lifestyle. Although there is substantial improvement in the quality of material conditions, lifestyle shifting increases the likelihood of exposing to stress, to have sedentary jobs, to increase energy intake, and to reduce levels of physical activity [8–10], leading to overweight, obese, and metabolic syndrome and high burden of EMD [11]. Such massive socioeconomic impact on EMD will be a typical example of period effect in epidemiology. Historically, China had been greatly affected by the war before 1949. Medical care was not available to the general public, and there was a lack of effective treatment measures for EMD. After the founding of the People's Republic of China (PRC) in 1949, an innovative primary healthcare system and the market-oriented economic reform were implemented, which greatly improved the health of Chinese by providing early diagnosis, treatment, knowledge of disease prevention and personal hygiene [12–14]. Consequently, in addition to period effect, we anticipate a further volatility in the risk of EMD annual mortality with period-cohort effect.

Understanding the period and cohort effect of socioeconomic growth and healthcare systems and their relationship with the risk of EMD is of great significance for public health planning and decision-making. However, no developing countries, including China, have ever collected historical data about EMD annual mortality until recent years. Nevertheless, annual mortality data by age contain historical information regarding the risk of death. For example, the mortality for all people in 1990 who aged 80 also contains information about risk of dying during the 80-year period for this cohort since their birth in 1910. This study extracts such information with advanced methods.

Among different methods, the age-period-cohort (APC) analysis provides an approach to disentangle the age, period and cohort effects using multi-year mortality data [15, 16]. Age effect is referred to variations in mortality risk by age or changes in the risk of dying from EMD along with the biological development across life span. Period effect is referred to risk of mortality due to massive social, economic, technological, healthcare systems that affect all people simultaneously regardless of their ages. Cohort effect is referred to variations in mortality risk by birth cohort, reflecting the initial and accumulative exposure of a cohort to EMD risk. When mortality data are tabulated by age, APC models can be constructed to estimate age, period, and cohort with recent data [17].

APC analyses have been used in investigating vital rates for many diseases, including cancers and infectious diseases [17–19]. However, no reported study has used this method to analyze EMD annual mortality data in China. The purpose of this study is to investigate the secular trends and rural-urban differences in EMD annual mortality in China during 1991 to 2016.

This APC model decomposes a mortality rate of a specific year of a population to the risk related to current year (period effect), year of birth (cohort effect), and biological age (age effect). Although we have no data regarding the risk of EMD before 1991 in China, with the APC modeling method and the 1991–2016 annual mortality data, we can obtain the information regarding the risk of EMD death trace back to 1911, a time span of 100 years. Linking the estimated period effect and cohort effect with socioeconomic growth, lifestyle change, and healthcare development will shed light on the impact of these factors on the risk of EMD death after allowing for the age effect.

Material and methods

Data source and collection

The annual mortality rates (/100,000) by 5-year age-group from 5 to 84 years old between 1991 to 2016 were extracted from the Health Statistics Yearbook of China. The ICD-10 code (the 10th version of the International Statistical Classification of Diseases and Related Health Problems) was used to classify the cause of death, and the code of E00-E88 was used to represent the endocrine, nutritional, and metabolic diseases. The analysis was restricted to deaths from ages 5 to 84 with a total of 16 age-groups. The youngest age-group 0–4 was excluded because of lacking precise data, while the oldest age-group 85+ years was also excluded because open-ended age data were unsuitable for APC modeling analysis. Thus, the final data consisted of 16 five-year age-groups (from age 5–9 years to age 80–84 years), 6 periods (from 1991 to 1995 to 2011–2016), and 21 five-year birth cohorts (from the 1911–1915 cohort to the 2011–2016 cohort). Data for rural and urban areas were analyzed separately for further comparisons.

Age-period-cohort modeling

We constructed APC models to extract the age effect α, time period effect β, and birth cohort effect γ from the documented mortality of EMD (r_{ijk}). The following log-linear model was used:

$$\log(r_{ijk}) = u + \alpha_i + \beta_j + \gamma_k$$

where u was the intercept, α_i was the age effect (i = 5–9, 10–14, 15–19, 20–24, …, 80–84), β_j was the period effect (j = 1991, 1992, 1993, …, 2016), and γ_k was the cohort effect (k =

1911–1915, 1916–1920, …, 2011–2016).

Although the APC model is powerful, it is statistically not identifiable due to the complete collinearity among the three predictors age, period, and cohort as cohort = period - age [16]. Thus, Intrinsic Estimator method, which was capable of obtaining unique solution to APC model was used in the study [20]. The IE method has been proved to be mathematically estimable, unbiased, valid, and asymptotically consistent [20] and used by other researchers in APC modeling research [19, 21], including research of analyzing Chinese mortality data on different health issues [18, 22].

We conducted the APC modeling analysis using the package apc_ie with Stata/SE version 12. Model coefficients and standard errors were computed. Data-model fit was assessed using deviance (DV), Akaike information criterion (AIC), and Bayesian information criterion (BIC). For comparison purpose, modeling analysis was conducted for rural and urban separately. To visualize the trends of age, period, and cohort, the estimated model coefficients were plotted with year.

Results

Descriptive analysis

Figure 1 presented the annual mortality rates of EMD from 1991 to 2016 in China. Overall, both urban and rural annual mortality rates have a sharp rise during the past 26 years. The mortality rate for rural areas increased from 5.25 per 100,000 in 1991 to 20.43 per 100,000in 2016 (289.1% increase), while the same rate for urban area increased from 10.07 per 100,000 in 1991 to 20.43 per 100,000 in 2016 (102.9% increase). And annual mortality from EMD in urban has been consistently higher than that in rural area.

Age-specific EMD annual mortality rates by period and cohort were drawn respectively in Figs. 2 and 3 to grab a visual impression of the age, period, and birth cohort effects. Figure 2 shows the age-specific EMD annual mortality rates by period. The annual mortality rose with age whether in urban or in rural area. The annual mortality of urban increases rapidly between 1996 and 2006 and reaches a maximum in elderly (age 80–84) in 2006. By contrast, the age-specific EMD annual mortality of rural seems to be increasing year by year and maximizes in ages 80–84 in 2016.

Figure 3 displayed the age-specific EMD annual mortality rates by birth cohort. The annual mortality in different birth cohort has no obvious regulation. The annual mortality from EMD for urban and rural residents reaches maximum in cohort 1926–1930 and cohort 1936–1940 respectively for urban and rural areas. Overall, later birth cohorts have gone through lower mortality risk when compared to those birth earlier. The differences between different birth cohort in rural were bigger than differences in urban.

Age, period, and birth cohort effects

Parameters estimated by Intrinsic Estimator for APC model are listed in Table 1. The relative risk [6] of a particular age, period, or birth cohort relative to average levels was calculated by the following formula: $RR = e^{coef.}$(Table 1).To grasp age, period, and cohort effect trends more intuitively, we plotted Fig. 4 based on the relative risk.

Age effects

Results in the upper panel of Table 1 and Fig. 4a indicated a *J*-shaped pattern of the age effects. The risk declined to the lowest level at age-group 10–14, then a flat base up to 30–

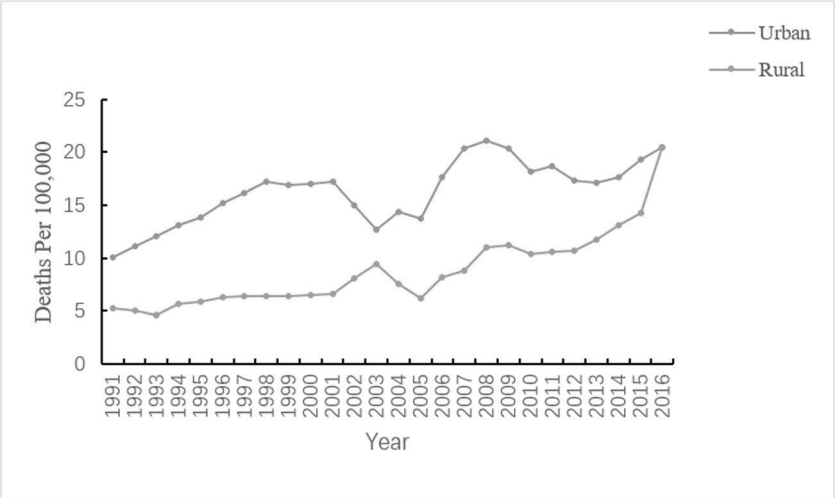

Fig. 1 Trends of the annual mortality rate of the endocrine and metabolic diseases of Chinese rural and urban residents, 1991–2016

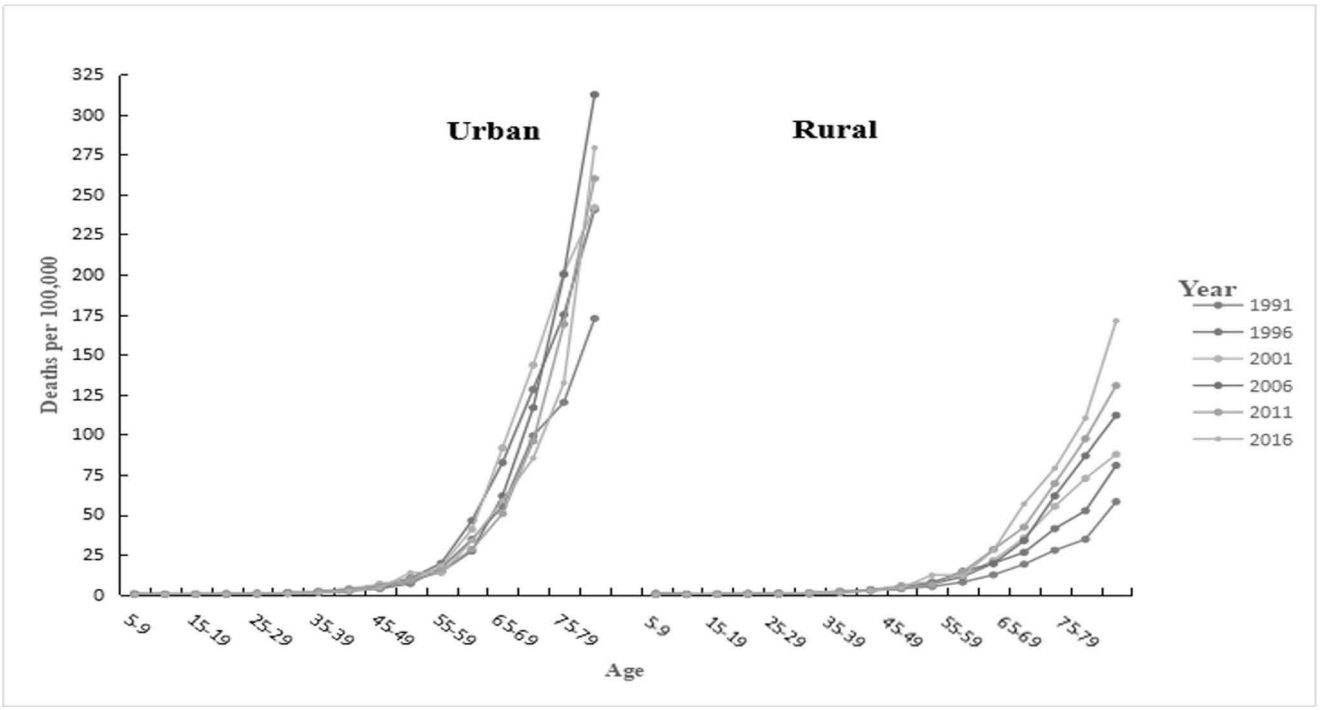

Fig. 2 Age-specific endocrine and metabolic diseases annual mortality rates by period of Chinese urban and rural residents, 1991–2016

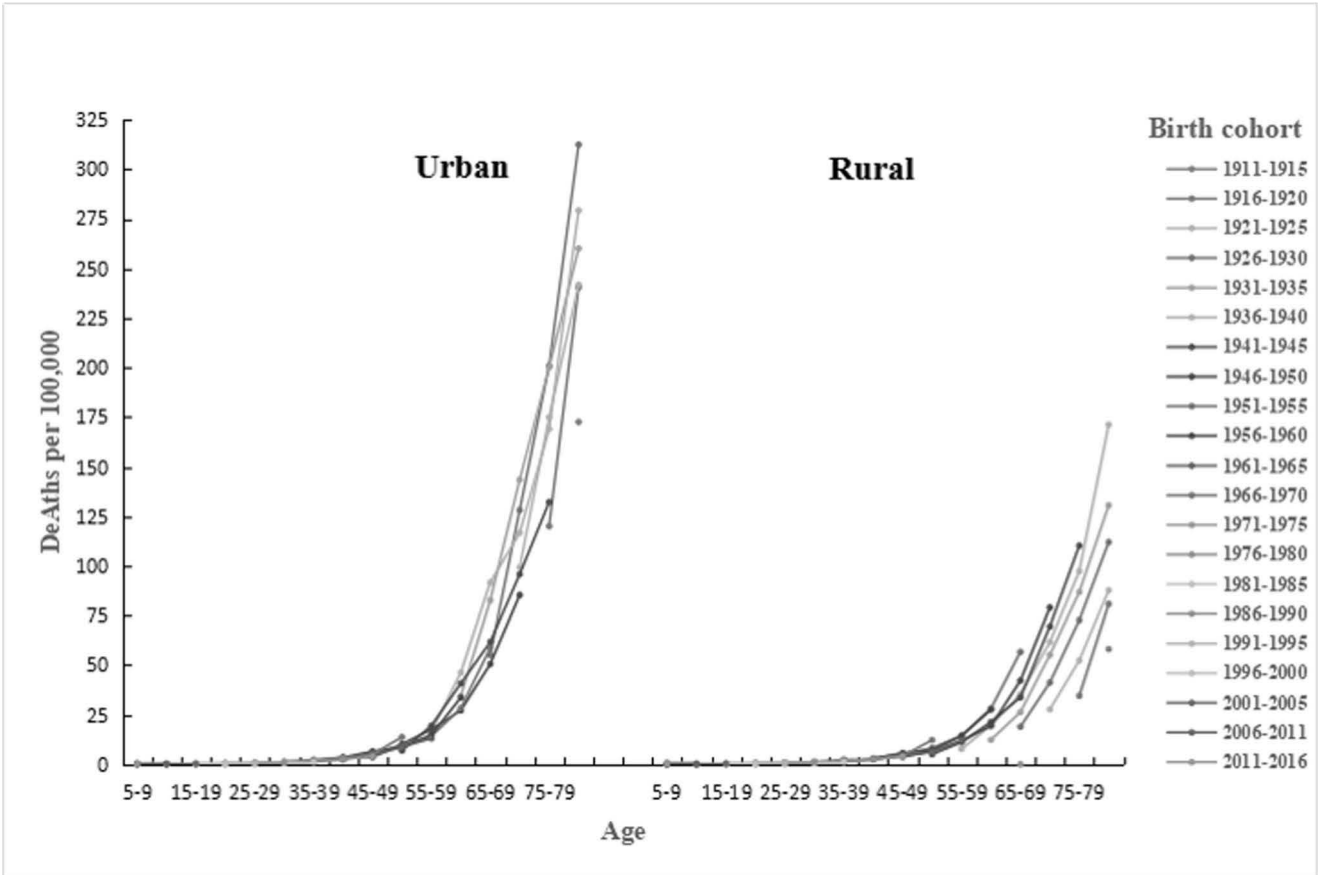

Fig. 3 Age-specific endocrine and metabolic diseases annual mortality rates by birth cohort Of Chinese urban and rural residents, 1991–2016

Table 1 Results of APC modeling analysis of the endocrine and metabolic diseases annual mortality for rural and urban areas in China

	Urban			Rural		
	Coef.	SE	RR	Coef.	SE	RR
Intercept	1.478	0.192		1.088	0.212	
Age						
5–9	− 1.611	0.823	1	− 1.135	0.773	1
10–14	− 2.096	0.870	0.616	− 1.775	0.867	0.527
15–19	− 1.968	0.751	0.700	− 1.616	0.716	0.618
20–24	− 1.844	0.657	0.792	− 1.585	0.621	0.638
25–29	− 1.765	0.566	0.858	− 1.509	0.528	0.688
30–34	− 1.384	0.467	1.255	− 1.311	0.459	0.839
35–39	− 1.029	0.393	1.790	− 0.953	0.383	1.200
40–44	− 0.622	0.320	2.688	− 0.694	0.316	1.555
45–49	− 0.165	0.256	4.246	− 0.286	0.254	2.337
50–54	0.381	0.197	7.333	0.128	0.205	3.536
55–59	0.800	0.159	11.149	0.566	0.170	5.482
60–64	1.432	0.133	20.973	1.092	0.149	9.271
65–69	1.936	0.139	34.718	1.604	0.155	15.472
70–74	2.335	0.168	51.716	2.128	0.182	26.131
75–79	2.632	0.209	69.660	2.478	0.222	37.069
80–84	2.968	0.257	97.410	2.868	0.267	54.766
Year						
1991	− 0.397	0.149	1	− 0.443	0.155	1
1996	− 0.039	0.092	1.429	− 0.125	0.102	1.375
2001	0.056	0.046	1.573	0.016	0.063	1.582
2006	0.098	0.047	1.639	0.056	0.060	1.647
2001	0.067	0.093	1.590	0.161	0.096	1.830
2016	0.215	0.145	1.843	0.336	0.144	2.180
Birth cohort						
1911–1915	1.102	0.317	1	0.551	0.333	1
1916–1920	1.076	0.260	0.975	0.518	0.273	0.968
1921–1925	1.057	0.211	0.957	0.516	0.226	0.966
1926–1930	1.141	0.168	1.041	0.692	0.186	1.152
1931–1935	1.067	0.136	0.966	0.780	0.158	1.258
1936–1940	0.954	0.123	0.863	0.855	0.145	1.356
1941–1945	0.628	0.141	0.623	0.825	0.162	1.315
1946–1950	0.420	0.178	0.506	0.827	0.194	1.318
1951–1955	0.395	0.225	0.493	0.994	0.236	1.558
1956–1960	0.369	0.279	0.481	0.820	0.289	1.309
1961–1965	0.177	0.342	0.397	0.509	0.354	0.959
1966–1970	0.378	0.390	0.485	0.740	0.396	1.209
1971–1975	− 0.082	0.478	0.306	0.290	0.475	0.770
1976–1980	− 0.306	0.558	0.245	0.016	0.550	0.586
1981–1985	− 0.565	0.650	0.189	− 0.438	0.665	0.372
1986–1990	− 0.628	0.673	0.177	− 0.304	0.632	0.425
1991–1995	− 0.714	0.754	0.163	− 0.551	0.731	0.332
1996–2000	− 1.496	1.148	0.074	− 1.276	1.051	0.161
2001–2005	− 1.395	1.242	0.082	− 1.964	1.570	0.081
2006–2011	− 1.782	1.736	0.056	− 2.071	1.869	0.073
2011–2016	− 1.796	2.366	0.055	− 2.329	2.735	0.056

Table 1 (continued)

	Urban			Rural		
	Coef.	SE	RR	Coef.	SE	RR
Deviance (df = 56)	13.994			5.878		
AIC	4.555			4.207		
BIC	− 241.610			− 249.725		

Note: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; Coef., coefficient; SE, standard error; RR, relative risk; AIC, Akaike information criterions; BIC, Bayesian information criterions

34, followed by almost a steady increase to the last age-group. The risk for rural residents was higher than for urban residents between age-group 5–9 to age-group 30–34; this pattern was reversed after 35 years old. Compared with the youngest age-group (5–9) in urban and rural, the oldest age-group was faced with a 97.410 and 54.766 times risk correspondingly.

Period effects

Results in the middle panel of Table 1 and Fig. 4b indicated that the risk of EMD death by period had a continued growth from 1991 to 2016, with a more rapid increase before 1996 and after 2001. With the estimated *RR* in 1991 as the references, mortality risk related to period effect increased to 118.0% for rural and 84.3% for urban areas respectively. The risk of urban areas increased quicker than that in rural areas during 1991–2005 before a reverse pattern appeared during 2006–2016.

Cohort effects

Data in the lower panel of Table 1 and Fig. 4c indicated that the estimated birth cohort effect during 1911–2016 showed a pattern opposite to the period effects. Overall, there was a progressive decline in the mortality risk along with the advancement of birth year over the 100-year period. Relative to cohort 1911–1915, the relative risk for the most recent cohort was 0.055 [exp(−1.996–1.102)] for urban and 0.056 [exp(−2.329–0.551)] for rural. The birth cohort-related risk of death for urban areas declined progressively with some fluctuations, while the same effect for rural areas increased for people born between 1911 and 1955 before it declined. The cohort effect declined quicker for rural residents than for urban residents after 1956. Lastly, there was an increase in cohort effect for urban residents born during 1996–2005.

Discussion

In this study, we analyzed the annual mortality rates of EMD during 1991–2016 in China with the APC modeling. And the advanced intrinsic estimate algorithm is performed to calculate the parameters. Findings of this study are the first to obtain continuous mortality information for rural and urban residents during 100 years with recent data in the past 20 years.

A better predictor for EMD risk: period effect

Mortality of EMD by year has been used conventionally to describe changes in the risk of death over time, but findings of this study suggest that the period effect estimated from APC modeling was a better measure of mortality risk. The period effect was measured after controlling the effects from chronological age and birth cohort, both of which were significantly associated with the mortality rate by year. Relative to the annual mortality, changes in the period effect better characterized changes in EMD risk, which increased quickly before the second healthcare reform to increase insurance coverage during the later 1990s and early 2000s [23]. This pattern has not been captured by the annual mortality rate during the period. According to the period effect, the mortality for rural area increased quicker in more recent years than earlier times, and there was no sign of decline in the mortality for both rural and urban area since 2001, given the healthcare reform.

Difference between rural and urban

From 1911 to 1955, the cohort effect increased for rural residents and declined for urban residents in China. Given the backward economy, wars and disasters year by year during this period, the rural-urban differences in cohort could be primarily due to the rural-urban difference in medical and healthcare. Modern medicine was brought into China and began to boom in the early nineteenth century [24]. The Nationalist government established the Department of Health Care under the Ministry of Health to take charge of EMD care in 1928 and also established the healthcare system in provinces [25]. However, health policies and medical institutions were mainly covered in urban [26]. The inequality in resource distribution and in access to services between rural and urban led to higher overall prevalence, mortality, and lower attendance rate among rural residents than urban residents

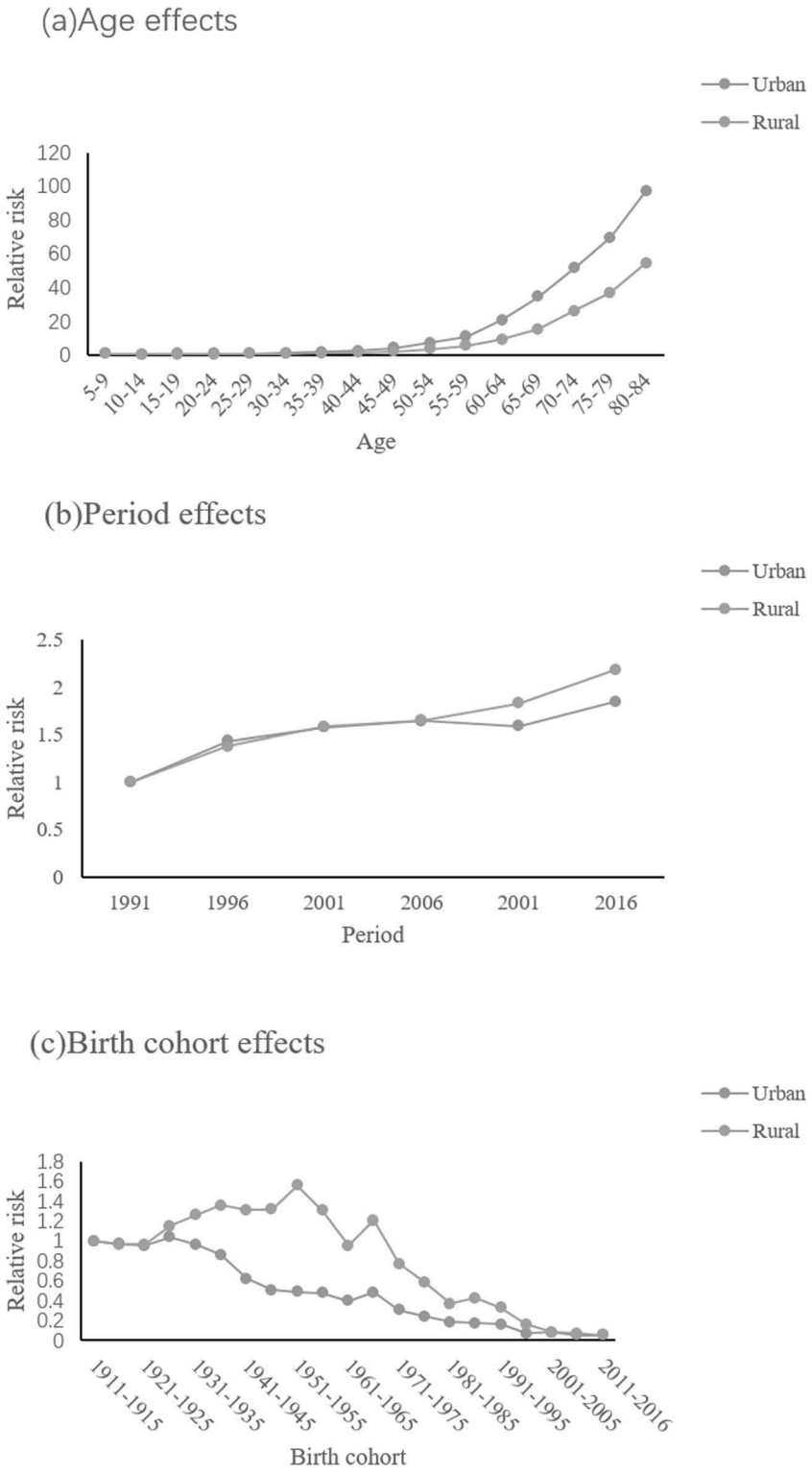

Fig. 4 Age, period, and birth cohort effects of endocrine and metabolic diseases annual mortality of Chinese urban and rural residents, 1991–2016. **a** Age effects. **b** Period effects. **c** Birth cohort effects

[26]. Thus, the trend of EMD mortality in rural was opposite to that in urban.

The urban-rural differences in the cohort effect after 1955, that was the birth cohort-related risk of EMD death declined quicker for rural residents than for urban residents, could be a combination of both lifestyle and healthcare. The dual-system society put rural residents at low socioeconomic level so that rural residents were less likely than urban residents to adapt unhealthy sedentary lifestyles and EMD diet. In addition, health policies emphasizing rural health during the periods

1960–1980 [27] and current health reform for rural areas [28] may increase the chances for rural patients to receive care, reducing mortality. The sudden acceleration in cohort effect during the 1996–2005 period at urban area was associated with large-scale marketization of nationally owned industries [29] and marketization of healthcare, which prevented many patients from receiving even minimum healthcare, increasing the risk of death overall [30], including EMD.

The new challenge for public health

Although the cohort effect of EMD annual mortality decreased, the annual mortality rate of EMD increased during the period from 1991 to 2016, suggesting potential increases in EMD in the future. More urgent measures are needed to reduce the incidence of EMD and to reduce the mortality after people get sick. Evolving integrated healthcare system and keeping healthy lifestyle are critical measures. On one hand, even though the PCR had launched the new medical reform in 2009, and committed to providing affordable basic healthcare for all Chinese people by 2020, several problems remained to be worked out [31]. On the other hand, researches had confirmed that EMD could be successfully addressed through population-wide interventions and policy strategies to improve diet, increase physical activity, and reduce sugar intake [32]. However, unhealthy lifestyle behaviors such as too much sugar intake, lack of practice, and other unhealthy diet are still common among people in China [33]. It is of great importance that translating researchers' findings into practice in health systems and public policies so as to reduce unhealthy behaviors among high-risk individuals.

There are three limitations of this study. First, results providing by APC model are macro. Such results cannot be treated as causal but can be used as guidance for more in-depth research to draw causal conclusion. Second, data used for this study were derived from death report. There is a significant possibility to ignore underreport and misreport part. Last but not the least, we cannot obtain annual mortality data for individual EMD, particularly diabetes. Although reported data indicate that diabetes disease accounts for more than 90 % EMD of death [7], we cannot use the findings of this study to forecast the mortality risk of diabetic mellitus.

Conclusions

We analyzed the age, period, and cohort effects of Chinese residents' EMD annual mortality by APC method. Generally, significant age, period, and cohort effects on EMD mortality risk were observed in both rural and urban China. The mortality risk increased exponentially with age, rose with period, and decreased with cohort. Above findings indicate that period effect may be a better indicator than annual mortality rate to assess risk over time. The difference between rural and urban in cohort effect of EMD mortality suggests the influence of unhealthy lifestyles and insufficient healthcare coverage. And the increase of period effects shows new challenges for China's public health and deserved to be focused on.

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Acquisition, analysis, or interpretation of data: Ying Li and Qi Pan.
Drafting of the manuscript: all authors.
Critical revision of the manuscript for important intellectual content: all authors Statistical analysis: Ying Li, Lixin Guo, and Hong Yan.
Administrative, technical, or material support: all authors.
Study supervision: all authors.

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ORIGINAL ARTICLE

Care burden and quality of life in mothers of children with type 1 diabetes mellitus

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Abstract

Purpose This was a descriptive study to determine the care burden and quality of life of mothers of children with type 1 diabetes mellitus (T1DM) and the correlation between these two variables.

Methods The sample consisted of 106 mothers of children with T1DM. Data were collected using a descriptive questionnaire, the Zarit Caregiver Burden Interview and WHOQOL-BREF quality of life scale, and were evaluated with the Mann-Whitney *U* test, Student's *t* test, ANOVA, Kruskal-Wallis test and Spearman's correlations.

Results Mothers had a moderate burden level (34.95 ± 12.48) with a statistically significant difference between income state and care burden ($p < 0.05$). Environment-related quality of life was related to income and physical quality of life was related to the time of diagnosis ($p < 0.05$). Care burden was negatively correlated with some aspects of quality of life. These results imply that mothers of children with T1DM have a moderate care burden and that their care burden has a negative impact on their quality of life.

Conclusions It may be provided to support the systems and suggested applying experimental studies due to decreasing care burden and increasing the quality of life of mothers who have children with T1DM in terms of gaining better care for children with T1DM.

Keywords Type 1 diabetes mellitus · Child · Mother · Care burden · Quality of life

Introduction

Type 1 diabetes mellitus (T1DM) is increasing in prevalence worldwide. It is a chronic disease with biological, psychological and social effects and affects the families of children with T1DM as well as the children themselves [1]. Management of T1DM is a complicated and challenging process involving regulation of diet, exercise, insulin injections and monitoring of blood glucose levels using a glucometer/insulin pump [2].

It is known that caregivers of children with T1DM have problems, such as the change in routine that a diagnosis entails, the extra cost of drugs and medical equipment, economic distress, devoting more time for caring of children, poor sleep, dealing with the stigma of having a child with T1DM, increased responsibilities, the extra effort required at home to prevent the child's symptoms from deteriorating and psychological tension (stress, suppression, anxiety, sadness and desperation) [3, 4]. The World Health Organization (WHO)'s report on diabetes noted that diabetes and its complications place a significant economic burden on individuals diagnosed with diabetes and their family because of health care expenses and loss income. [5].

Although having a child with T1DM is very stressful for all family members, primary caregivers bear the heaviest burden [6]. In most cases, the child's primary caregiver is the mother [7]. A study of parents of children with T1DM found that mothers had a higher perceived care burden than fathers due to medical treatment and emotional stress [8]. Mothers stated that they had to rearrange their work schedule or quit their job in order to manage their child's diabetes and that they had economic problems [9]. Furthermore, mothers of children with T1DM defined caregiving as "the change of life and run out of everything" and "always being alert". They also feel overwhelmed, because they have to police their child's

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food and timing of meals and exercise and are often sole caregivers [10]. Another study conducted with parents of children with T1DM reported that mothers experienced more anxiety than fathers, that the life of most parents changes after the child's diagnosis and that most feel overwhelmed by the demands of diabetes care and the complications of the disease. Perceived care burden was related to parents' anxiety and depression [7]. There is, however, limited information about the quality of life and care burden in mothers of children with T1DM [3, 4, 8]; there has been no research evaluating the relationship between mothers' care burden and quality of life. This descriptive study sought to fill this gap.

Materials and methods

Design and sample

This was a descriptive study to determine the care burden and quality of life of mothers of children with T1DM and the correlation between these variables. It was carried out in an endocrinology polyclinic of a university hospital located in Central Anatolia. The participants were mothers who had a child that had been diagnosed with T1DM at least a year ago and had no other diseases except T1DM, who undertook primary care of that child and were not the carer for anyone else with a chronic disease and agreed to participate. The sample size was calculated as 112 based on a study about care burden scores in caregivers of chronic obstructive pulmonary disease patients performed by Tel et al. [11] by predicting effect size as 0.27, type 1 error as 0.05 and power as 80%. In this study, 112 mothers were reached and 6 mothers were excluded due to the lack of data collection form and study was completed with 106 mothers. Post-power analysis of the study was calculated as 85% with 106 participants. Data were collected from mothers between January and July 2016 by using a descriptive questionnaire, the Zarit Burden Interview and WHOQOL-BREF quality of life scale.

Instruments

Descriptive questionnaire

The descriptive questionnaire consisted of 27 descriptive questions (mother's age, mother's education, mother's profession, income state, home place, child's age, sex of the child, information about T1DM management and treatment).

Zarit burden interview

This scale was developed by Zarit et al. [12] and its validity and reliability in the Turkish population were demonstrated by İnci and Erdem [13]. It comprises 22 statements about the effect of caregiving on the life of the respondent and responses are given using a 4-point Likert scale. Scores range from 0 to 88, with higher scores indicating a higher burden of care. Several categories of burden have been defined on the basis of scores on the scale: 61–88 points indicate an overload, 41–60 points a high burden, 21–40 points a moderate burden and < 21 points a low or negligible burden [13].

WHOQOL-BREF quality of life scale

The WHOQOL-BREF scale was developed by WHO and its validity and reliability in the Turkish population were demonstrated by Eser et al. [14, 15]. The scale consists of 26 questions organised into four subscales (physical, social, psychological and environmental). Responses are given using a 5-point Likert scale. The maximum score for the subscales varies between 4 and 20. No overall score is calculated. Higher subscale scores indicate better quality of life.

Ethical considerations

The study was approved by the local ethical committee (code of ethical approval, 2015/182) and the participating institution, and written consent was obtained from the mothers.

Data analysis

Descriptive statistics (percentages, means, standard deviations, medians and minimum and maximum values) were calculated. The normality of variable distributions was examined with the Shapiro-Wilk normality test. The independent-samples t test or Mann-Whitney U test was used for comparison of two independent groups, depending on whether the data were normally distributed. ANOVA or the Kruskal-Wallis test was used for comparison of more than two independent groups. Spearman's correlation analysis was used for binary categorical comparison. The level of statistical significance was set at $p < 0.05$.

Results

The majority of mothers (58.5%) were aged between 31 and 40 years, 84.0% of participants were homemakers, 61.3% had a balance in income and expenses and 17.0% had a chronic illness. Most of the children with T1DM (68.9%) had been diagnosed at least 3 years ago, 18.9% were aged 0–6 years old, 38.6% were aged 7–12 years and 42.5% were aged over 12 years, 50.0% were male, and 84.0% used insulin four times a day. With regard to the management of the child's diabetes, 11.3% checked their blood glucose level unaided, 5.7% arranged their diet by themselves and 14.2% were responsible for their own insulin injections, an important aspect of T1DM

management. Considering the characteristics related to care needs of children with T1DM, it was determined that of mothers, 69.8% were interested in day care while 30.2% were interested in child care in the night time. Most of the mothers (90.6%) stated that their social roles (77.4%), family role (73.6%) and work role (22.6%) were adversely affected by their child's illness.

The mothers' mean care burden score was 34.95 ± 12.48. Mean quality of life scores were as follows: physical, 13.92 ± 2.69; psychological, 13.45 ± 2.55; social, 12.95 ± 3.66; and environmental, 12.91 ± 2.03 (Table 1). These scores suggest they had a moderate care burden and quality of life. All aspects of quality of life were negatively correlated to care burden ($p < 0.05$). In other words, considering scores of care burden scale and quality of life scale mean scores, it was determined that mean scores of subscales of quality of life scale decreased as mean scores of care burden increased ($p < 0.05$) (Table 2).

The mothers had a significantly higher care burden if they were aged 41 years and older, only educated to primary level, had a chronic illness, had a child with T1DM aged 0–6 years or had a child who had been diagnosed 3–4 years ago. Mothers whose income exceeded their expenditure had the lowest care burden ($p < 0.001$). Physical quality of life was not related to the mother's age, education level, chronic illness status, income or family size, nor to the age or sex of the child with T1DM. Physical quality of life was lower in mothers whose child had been diagnosed with T1DM 3–4 years ago ($p = 0.022$). Psychological and social quality of life were not related to the mother's age, education level, chronic illness status, income or family size, nor to the age or sex of the child with T1DM, nor the time since diagnosis. Environment-related quality of life was not related to the mother's age, education level, chronic illness status or family size, nor to the age or sex of child with T1DM, nor to the time since diagnosis. We also found that women with a high income had better environment-related quality of life ($p < 0.001$).

Table 1 Means of care burden and quality of life scale of mothers ($n = 106$)

Scales	Mean ± SD	Minimum–maximum
Care burden scale*	34.95 ± 12.48	0.00–88.00
Quality of life scale*		
Physical	13.92 ± 2.69	4.00–20.00
Psychologic	13.45 ± 2.55	4.00–20.00
Social	12.95 ± 3.66	4.00–20.00
Environment	12.91 ± 2.03	4.00–20.00

*Higher scores denote a higher care burden and a better quality of life

Table 2 Correlation of care burden and quality of life scale of mothers of children with T1DM

Scales	Quality of life scale			
	Physical	Psychologic	Social	Environment
Care burden scale	$r = -0.239$ $p = 0.013$	$r = -0.205$ $p = 0.035$	$r = -0.336$ $p = 0.000$	$r = -0.394$ $p = 0.000$

Discussion

Having diabetes affects all aspects of life as it requires constant monitoring and regulation of blood glucose levels, dietary regulation and regulation of activities compatible with them. The parents of children with T1DM should help their child to manage his or her illness and take some of the responsibility for doing so. We found that mothers of children with T1DM have a moderate care burden and take responsibility for insulin administration, monitoring of blood sugar level and dietary regulation or share these responsibilities with the child who has T1DM. Most of the mothers in our study reported that their family, social and work roles were badly affected by their child's illness. This suggests that mothers who have a child with T1DM have additional care responsibilities, their care burden increases as a result of their child's illness and this has a negative impact on their quality of life. A study of the parents of children with T1DM found that 50.5% of mothers took responsibility for caring of the child with T1DM, a figure similar to that obtained in our study. Most parents in this earlier study reported that their family life had changed after their child was diagnosed with T1DM and said that they were concerned about possible complications and they felt burdened by their child's T1DM [7]. Yet another study of mothers of children with chronic renal failure, epilepsy or T1DM found that the mothers of children with T1DM had the highest burden of care [16]. Our findings are consistent with previous research in this area and suggest that the mothers of children with T1DM should receive counselling and/or psychological and economic support to help them cope with their increased care burden.

Chronic illnesses are known to impose a heavy economic burden on families, due to the need for long-term care, monitoring, follow-up and supervision [17]. The WHO's 2016 diabetes report stated that diabetes and its complications constitute an important economic burden on patients and their families due to the health care costs of diabetes and the loss of earning capacity [5]. A study that examined the factors affecting the burden on caregivers of children with T1DM found a negative relationship between care burden and economic situation [18]. An integrative review of the care burden and quality of life of mothers of children with chronic diseases and adolescents concluded that the burden of care was increased by lack of money, unemployment and changes in

professional life [19]. Our results are consistent with the literature we found that burden of care was related to family income. It has also been reported that the burden of care is affected by parental occupation and education level, the number of children in the family and the age of the sick child [4, 19], but we found that the mother's age, education level and family size and the age of the child with T1DM did not affect the burden of care. This may be due to the fact that the mothers in our study were not caring for anyone else with a chronic illness, the children with T1DM did not have other medical problems and most of the mothers were homemakers.

In a study, it was stated that the care burden is the highest in the first 1–4 years after diagnosis [20] and there are others showing that the care burden increases over time [21]. We found that mothers' burden of care was not related to the length of time for which their child had had T1DM. This may be because T1DM requires life-long management and regular monitoring, and in the case of children, the burden of management falls mainly on the primary caregiver, who is usually the mother.

It has been reported that the care burden of caregivers of individuals with chronic illnesses is negatively correlated to their quality of life [19, 22, 23] and our results corroborate these findings. We also found that mothers' economic quality of life was related to their economic situation. Noueiri and Nassif stated that economic problems negatively affected the quality of life of families of children with T1DM [24]. Families with a high income are more likely to be able to cope with the financial burden of chronic illness. We also found that mothers' physical quality of life was related to the length of time since their child was diagnosed with T1DM, being lowest in mothers whose child had had T1DM for 1–2 years or at least 5 years. We suggest that this result reflects the extra difficulty of managing the disease in the first 1–2 years after diagnosis and the burnout related to the difficulty of living with the disease over the long term. Jönsson et al. found that parents'—particularly mothers—quality of life was badly affected in the first year after their child was diagnosed with T1DM [25]. Previous studies have also noted that difficulties with diabetes management and concerns about potential complications also have negative effects on parents [20, 26].

Conclusions

Our findings suggest that the primary caregivers of children with T1DM, usually the mother, should be directed to institutions and organisations that can offer support with the management of T1DM (checking blood sugar, insulin injections, having control sessions, diet, exercise), education and counselling. It might be helpful to offer support programmes for children with T1DM, and it would be worth carrying out experimental research on the management of illnesses like T1DM and how they affect family members.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical considerations The study was approved by the local ethical committee (code of ethical approval, 2015/182) and the participating institution, and written consent was obtained from the mothers.

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ORIGINAL ARTICLE

Health-related quality of life of Pakistani adolescents with type 1 diabetes and their parents

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Abstract

Objective To assess the health-related quality of life of Pakistani adolescents with type 1 diabetes mellitus and their parents.

Methodology This cross-sectional study of adolescents with T1DM and their parents was conducted at Baqai Institute of Diabetology and Endocrinology, a tertiary care hospital, Karachi Pakistan from April 2017 to September 2018. Diabetes Quality of Life for Youths (DQOLY) questionnaire (assess possible problems in six dimensions of impact) and WHO QOL-BREF instrument was used to assess quality of life of adolescents with type 1 diabetes and their parents respectively. The data was entered and analyzed using IBM Statistical Package for Social Sciences version 20.

Results Adolescents with T1DM had adverse impact on their quality of life (QOL); overall QOL score was found 20.76 ± 0.83, the maximally reported adverse impact was related to symptoms of diabetes 24.35 ± 1.92 and impact of treatment 24.59 ± 2.12. Females had more adverse impact on QOL score, i.e. 22.49 ± 1.2 (p value = 0.015). Adverse effect on QOL score is strongly correlated with increasing age (p value = 0.006). Overall QOL score of parents/care takers was 56.3 ± 0.98. The worst overall QOL score was noted to be of care takers 53.75 ± 3.4 followed by mothers 54.52 ± 1.25 and fathers 60.56 ± 1.61 respectively (p value = 0.015); the environment domain was associated with statistically significance adverse impact on QOL of mothers (p value = 0.008).

Conclusion It is imperative for health care professionals to be aware of the effect of diabetes on QOL as timely screening is important for better health care outcomes.

Keywords Quality of life · Adolescent with T1DM · Parents

Abbreviations

T1DM	type 1 diabetes mellitus
NDSP	National Diabetes Survey of Pakistan
HRQOL	health-related quality of life
DQOLY	Diabetes Quality of Life for Youths
WHO QOL-BREF	World Health Organization Quality of Life Instrument

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Introduction

Type 1 diabetes mellitus (T1DM) is a metabolic disorder that is characterized by an immune-mediated exhaustion of beta-cells function resulting in chronic hyperglycemia and lifetime requirement of exogenous insulin for survival [1]. Onset can occur at any age, but a peak in incidence is witnessed around puberty [2].

Significant stress is contemporary in the affected children and their family especially in parents [3]. This is due to lifelong course of disease and multipronged management, including multiple daily insulin injections, fear of insulin, carbohydrates counting, self-monitoring of blood glucose (SMBG), keeping record of SMBG, dietary restrictions, cooking and eating healthy meals, exercising every day, and risk of short-term and long-term complications [4]. In developing nations like Pakistan, resource constraints, suboptimal health care system, unavailability of health insurance, lack of school health facilities, deprived health-seeking behavior in the society (due to cultural beliefs and perceptions, low literacy level of the mothers, and large family size), scarce rehabilitation center, future risk of job, marriage, risk of diabetes in offspring, and the societal stigma linked to the diagnosis of diabetes additionally exacerbate stress in children/adolescents with type 1 diabetes and their parents [5]. Patients with type 1 diabetes mellitus (T1DM) have to deal with a complex, multifaceted, and challenging daily treatment and exercise regimen that need motivation, passion, and lots of efforts [6]. The goal of treatment for type 1 diabetes is to keep blood glucose levels at optimum [7] to prevent or delay the onset of both short-term and long-term complications [8]..

Psychosocial factors play a vital role in the care and management of diabetes, according to the Consensus Guidelines of International Society for Pediatric and Adolescent Diabetes (ISPAD) [9]. To achieve the targeted goals, involvement of family members, bonding among them, and communication between them are crucial [10]. Diabetes-related stress is a disastrous condition because it has a negative impact on the health-related quality of life (HRQOL) of these patients which may lead to poor self-management of diabetes and failure of glycemic control [11, 12]. Proper metabolic control and adequate adherence to therapy may become more difficult to manage because of diminished insulin sensitivity and variety of other issues, such as family conflict and reduced parental participation in diabetes care during adolescence [13, 14]. Because of these factors, quality of life (QOL) of adolescents with type 1 diabetes and their parents is significantly affected including intensive treatment regimens along with psychosocial consequences (depression, anxiety, and/or social problems) [15, 16]. This area is under-researched in Pakistan. Thus, the aim of this study is to assess health-related quality of life of adolescents with type 1 diabetes mellitus and their parents.

Methodology

This cross-sectional study of adolescents with T1DM and their parents/caretakers was conducted at Baqai Institute of Diabetology and Endocrinology, Baqai Medical University, Karachi, Pakistan from April 2017 to September 2018. A total of 102 patients with already known type 1 diabetes aged 10 to 18 years and their parents (in case of unavailability of parents; care taker or guardian) who consented to participate were considered eligible. The questionnaires were administered to the patients with type 1 diabetes mellitus and their parents separately by diabetes educator who was assigned for data collection. Latest laboratory findings of the selected participants were retrieved from an electronic hospital database called Hospital Management System (HMS).

A short version of Diabetes Quality of Life for Youths known as DQOLY [17] questionnaire was used for the assessment of quality of life of adolescents with type 1 diabetes. This is a 22-item validated questionnaire to assess possible problems in six dimensions of impact, i.e. symptoms related to diabetes, treatment, activities, parents' issues, worry about the future, and perception of one's own health.

The responses were coded as 0, never; 1, sometimes; 2, regularly; 3, often; and 4, all the time. The raw score was calculated by totaling the figures of twenty-two answers. The raw score ranged from 0 to 88. A score of 0 represented the best possible while 88 represented the worst possible QOL.

WHO QOL-BREF [18] instrument which is a shorter and validated version of WHOQOL-100 was used to assess the quality of life of parents.

This instrument has 26 items that yield a generic HRQOL score across 4 broad domains: Physical health (7 items), Psychological health (6 items), Social Relationships (3 items), and Environment (8 items). There are two global scores: overall QOL (1 item) and overall satisfaction with health (1 item) and a third global score, namely global HRQOL, was obtained by averaging the two global items. In the instrument, questions are distributed and not organized domain-wise. The responses to items were noted on a 5-point Likert scale. Domain scores were scaled in a positive direction (higher scores denote better QOL), with a score range of 4–20 that were transformed to 0–100 scale according to the standard procedure defined in WHO QOL user manual. The data was entered and analyzed by using Statistical Package for Social Sciences (SPSS) version 20. Continuous variables were represented as mean ± SD or mean ± SE whereas categorical variables were represented in frequencies and percentages. Student's t test, ANOVA, and Pearson's correlation were used where applicable. Statistical significance was considered at p value < 0.05.

Results

We studied `102 adolescents with T1DM and their accompanying parent / caregiver. The parent / caretakers who participated in this study were fathers in 30.4% of cases (n=44) , mothers in 61.8% of cases (n=58) and caretakers in 7.8% (n=8) of cases (of which grandmothers n=2, maternal aunty n=1, elder brother n= 5) respectively. The mean age of adolescents with TIDM was 14.28 ± 2.73 years, among them 43.1% ($n = 44$) were male and 56.9% ($n = 58$) were female. The clinical and demographic features of study participants are summarized in Table 1.

It was observed that adolescents with T1DM had adverse impact on their QOL. Their overall QOL score was found 20.76 ± 0.83. Among the six subdomains of DQOLY, the maximally reported adverse impact was related to symptoms of diabetes 24.35 ± 1.92 and impact of treatment 24.59 ± 2.12, while the minimally reported was the health perception 1.29 ± 0.09.

The gender wise comparison of DQOLY questionnaire with mean ± SE is summarized in Table 2. Females had more adverse impact on QOL score, i.e. 22.49 ± 1.2 while male QOL score was 18.47 ± 1.02 (p value = 0.015). Adverse effect on QOL score is strongly correlated with increasing age (p value = 0.006) as shown in Fig. 1.

The comparison of QOL of fathers/mothers/care takers by using WHO QOL-BREF instrument with mean ± SE is presented in Table 3. Overall QOL score of parents/care takers was 56.3 ± 0.98 (higher scores denote better QOL). The worst overall QOL score was noted to be of care takers 53.75 ± 3.4 followed by mothers 54.52 ± 1.25 and fathers 60.56 ± 1.61 respectively (p value = 0.015). Among the four subdomains of WHO QOL-BREF, environment domain was associated with statistically significance adverse impact on QOL of mothers (p value = 0.008).

Table 1 Baseline characteristics of studied participants

Variables		n (%) or mean ± SD
Adolescents ($n = 102$)	Male	44 (43.1%)
	Female	58 (56.9%)
	Age (years)	14.28 ± 2.73
	Height (cm)	153.43 ± 10.47
	Weight (cm)	47.06 ± 11.28
	Body mass index (kg/m^2)	19.77 ± 3.41
	Duration of DM (years)	5.23 ± 3.92
	Ethnicity	
	Sindhi	4 (8.7%)
	Punjabi	2 (4.3%)
	Balochi	5 (10.9%)
	Pashtuns	6 (13%)
	Urdu speaking	24 (52.2%)
	Others	5 (10.9%)
	HbA1c (%)	9.78 ± 2.52
Relatives ($n = 102$)	Father	31 (30.4%)
	Mother	63 (61.8%)
	Others	8 (7.8%)

Table 2 Gender-wise comparison of QOL scores in diabetic adolescents

QOL domains	Male	Female	p value	Overall
N	44	58	–	102
Impact of symptoms	18.56 ± 2.68	28.74 ± 2.58	0.008	24.35 ± 1.92
Impact of treatment	21.21 ± 2.82	27.16 ± 3.02	0.166	24.59 ± 2.12
Impact on activities	3.52 ± 0.98	5.52 ± 1.38	0.271	4.66 ± 0.89
Parent issues	5.87 ± 1.64	9.2 ± 2.3	0.271	7.76 ± 1.49
Worries about DM	7.63 ± 1.77	11.02 ± 1.9	0.207	9.56 ± 1.33
Health perception	1.36 ± 0.13	1.24 ± 0.13	0.518	1.29 ± 0.09
Overall	18.47 ± 1.02	22.49 ± 1.2	0.015	20.76 ± 0.83

Data presented as mean ± SE

p value < 0.05 considered to be statistically significant

Discussion

The results of the present study suggested that nearly quarter of adolescents with T1DM had a significant adverse impact on QOL score due to their diabetes. Increasing age and female gender were associated with higher DQOLY scores, that is, with worse QOL.

The overall DQOYL score was 20.76 ± 0.83 in adolescents with T1DM. This finding is similar to Matziou et al.'s study [19] and Puri et al.'s study [5] that also noted mean DAWN QOL score 29.3. Moreover, QOL score was 18.47 ± 1.02 in male that was better than QOL score 22.49 ± 1.2 in female (p value = 0.015). This result is comparable with previous studies from developed [13, 14] as well as from developing countries [2, 19] that female gender has been noted to be related with greater negative impact on health-related quality of life [5]. There are six subdomains of DQOLY, i.e. impact of symptoms, impact of treatment, impact on activities, parent issues, worries about DM, and health perception [16]. Among the subdomains, the maximally reported adverse impact was related to the impact of treatment 24.59 ± 2.12 followed by the impact of symptoms of diabetes 24.35 ± 1.92 then worries about DM9.56 ± 1.33, parent issues 7.76 ± 1.49, and the impact on activities 4.66 ± 0.89, while the minimally reported was the health perception 1.29 ± 0.09.

In this study, the girls were observed to be more worried about their disease. This finding is similar to another study which noted that adolescent girls are more likely to admit negative emotions than their counterpart [16].

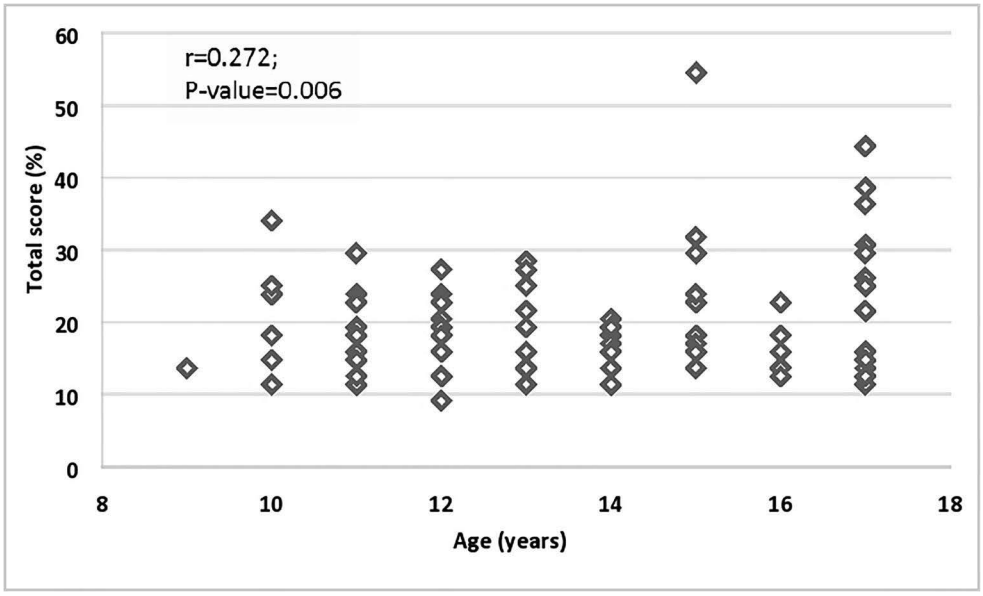

Fig. 1 Correlation b/w age and QOL score in adolescents

In gender-wise comparison of subdomains of DQOLY, regarding impact of symptoms domain, female had scored 28.74 ± 2.58 while male had scored 18.56 ± 2.68 (p value = 0.008), whereas other subdomains including impact of treatment, impact on activities, parent issues, worries about DM, and health perception of both genders were found statistically insignificant.

In our study, mean HbA1c of adolescents with T1DM was 9.78 ± 2.52%; this finding is similar to previous multiple studies [19–24] that poorer glycemic control is associated with overall worst QOL score. Increase in depressive symptoms is also associated with rising HbA1c [16]. Nevertheless, certain studies did not find any association between glycemic control and overall QOL [5, 20, 25]. Increasing age is also noted to be significantly linked with worse QOL (p value = 0.006), similar to a regional study [20, 24].

Adolescence is a time period of personal maturity and growth in which the individuals have to merge various disparate features of a sense of self into a new personality. This new personality includes a restructured image of body, new cognitive skills, a reviewed value system, and establishing a sense of adult independence. Due to this transition, adolescent may not be able to see clinicians' concerns over glycemic control as related to their daily needs for physiological and psychosocial well-being [14]. Although glycemic control should be the main focus of diabetes management, in addition great emphasis should be given to the quality of life and associated factors in young adults with T1DM. The DQOLY offers a convenient and reliable way to evaluate this important aspect of diabetes management as prevalence of depression in T1DM was noted to be as high as 42.3% according to our previous study [26]. Rendering to Australian guidelines, it is recommended that diabetes education programs must include knowledge-based evaluations, self-management, QOL, and psychological management to ensure the well-being of patients with type 1 diabetes mellitus [16].

WHO QOL-BREF [18] instrument is a shorter but validated version of WHOQOL-100 which was used to assess the quality of life of parents/care takers. This instrument has 26 items that yield a generic HRQOL score across 4 broad domains: Physical health, Psychological health, Social

Table 3 Comparison of QOL scores among relatives of diabetic adolescents

QOL domains	Father	Mother	Others	p value	Total
N	31	63	8	–	102
Physical health	55.29 ± 1.34	51.16 ± 1.41	55.63 ± 3.62	0.131	52.76 ± 1.01
Psychological	60.48 ± 1.86	58.38 ± 1.26	57.75 ± 4.35	0.611	58.97 ± 1.01
Social relationships	66.74 ± 3.11	57.97 ± 2.79	49.25 ± 9.26	0.059	59.95 ± 2.13
Environment	59.74 ± 2.25	50.59 ± 1.71	52.38 ± 4.17	0.008	53.51 ± 1.35
Overall	60.56 ± 1.61	54.52 ± 1.25	53.75 ± 3.4	0.015	56.3 ± 0.98

Data presented as mean ± SE

p value < 0.05 considered to be statistically significant

Relationships, and Environment (higher scores denote better QOL).

In our study, the overall QOL score of parents/care taker was 56.3±0.98. This is a similar finding to another study in which parents of T1DM reported statistically significant lower quality of life scores compared with Parents of non-diabetic teenagers [27]. Amongst them, overall score of care takers was 53.75 ± 3.4 (p value = 0.015) followed by score of mothers 54.52 ± 1.25 and score of fathers 60.56 ± 1.61 respectively. Among the four subdomains of HRQOL, social relationship domain was scored lowest by care takers who scored 49.25±9.26, (p value = 0.059), while mothers scored 57.97 ± 2.79 and fathers scored 66.74 ± 3.11 respectively.

The worst environment score was of mothers 50.59 ± 1.71 (p value = 0.008) followed by care takers 52.38 ± 4.17, and fathers 59.74 ± 2.25. Other two subdomains (physical health and psychological) were found to be statistically insignificant. Parents of adolescents with T1DM have a tendency to rate their child's quality of life somewhat lower than normal [28, 29]. Lower quality of life seems to be directly associated with depression, anxiety, and a negative family environment [26]. Many controlled intervention researches have been shown that family-based interventions using problem-solving skills training, collaborative parental involvement, and negotiation of diabetes management goals have led not merely to better regimen behaviors and metabolic control, but also to better-quality family relationships [13].

Parents of children with T1DM are more sensitive towards their children's illness and its associated complications. Moreover, societal stigma is attached to diabetes. Their overall QOL could be affected due to several worries. Parents are more concerned about complications of DM, uncertain professional life including educations, jobs, and career, and social issues like marriages, life expectancies, and chances of being parents of children with DM. All these factors affect QOL of parents/care takers of adolescents with T1DM.

This is a single centered study with relatively small sample size which is one of the limitations.

Conclusion

QOL of adolescents with T1DM and their parents is negatively affected. It is important for health care professionals to be aware of the effect of diabetes on QOL and their timely screening, and proper referral of identified persons for further counseling is important for better health care outcomes. Further large-scale multicenter studies are needed to validate our findings.

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Author's contribution Saima Askari: Concept, design, literature search, wrote, and approval of the final manuscript.

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Raheela Naseem: Interpretation of data, edited, and approval of the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Institutional review board statement Ethical approval was obtained by the Institutional Review Board (IRB) of BIDE with approval/reference number: BIDE/IRB/SASKARI/10/26/18/0216.

Informed consent statement Consent was taken from guardians or parents of children.

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ORIGINAL ARTICLE

Beliefs of Caribbean type 2 diabetes patients towards insulin therapy and prescription

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Abstract

Background and aim Previous research studies have shown that poorly controlled type 2 diabetes patients do not receive insulin therapy because of the resistance of the patients to insulin therapy. This study aimed to assess the belief of Caribbean insulin-naïve type 2 diabetes patients on insulin therapy.

Methods Five hundred ten insulin-naïve type 2 diabetes patients who have had diabetes for at least 5 years were recruited for a questionnaire interview. The questionnaire was a modified version of a previously validated research questionnaire. Data collected was analysed with SPSS software using chi-square to test for significances.

Results The majority of the patients have had diabetes for > 10 years and take > 2 different diabetes medications daily. About 67% and 81% of the patients do not believe that insulin therapy will cause them hypoglycemia and weight gain respectively. Similarly, a significant percentage does not believe that taking insulin will interfere with their normal lifestyle activities (72.2%, $p = 0.048$). Although a majority (64%) of the patients believe that taking insulin translates to personal failure in optimal blood glucose control, 90% do not believe that taking insulin will cause people to treat them differently. A majority of the patients do not believe that taking insulin will be helpful in preventing long-term diabetes complications (63.9%, $p = 0.001$), though 51% thought it would make them feel better.

Conclusion Contrary to several reports, this study shows that insulin-naïve Caribbean type 2 diabetes patients do not have a significant negative perception towards insulin therapy. This finding might be related to the socio-cultural background of the patients studied.

Keywords Type 2 diabetes · Glycemic control · Insulin therapy · Insulin prescription · Beliefs · Developing country

Introduction

Type 2 diabetes is the commoner type of diabetes in Trinidad and Tobago and worldwide, and research evidence from our laboratory and elsewhere has shown major challenges in optimally controlling the blood glucose levels of the affected patients [1–5]. This is essentially due to both defective insulin secretion and insulin action [6]. The United Kingdom Prospective Diabetes Study (UKPDS) has shown that at diagnosis most type 2 diabetes patients had only 50% of normal insulin secretion which decreases to 25% after 6 years of diabetes duration [6]. We have previously shown that poor glycemic control of type 2 diabetes patients in our population is related to several factors including poor dietary adherence, sedentary lifestyle and compliance with prescribed medications [1–3]. Other workers in other populations have shown that many type 2 diabetes patients with poor glycemic control who could have benefitted from insulin therapy did not receive it or did not receive it in a timely manner [7–10]. It has been argued that the high rate of poor glycemic control amongst type 2 diabetes patients is partly contributed by the resistance of the patients to insulin therapy [11]. Many studies in other populations have indicated that resistance to insulin prescription was related to beliefs and perceptions of type 2 diabetes patients [12–19]. A multinational study has shown that beliefs about insulin therapy are related to the cultures and health care systems of the different countries and complete understanding about the beliefs and perceptions of patients would require studies in their populations [11]. Indeed, studies in some developing countries have shown that type 2 diabetes

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patients do not adhere to prescriptions due to high cost of diabetes medications including insulin, and especially for patients without health insurance cover [20, 21]. Other studies have indicated that patients on insulin therapy deliberately omit insulin injection because of fear of gaining weight [22]. In Trinidad and Tobago, we do not have any data on the number of type 2 diabetes patients currently on insulin therapy nor the frequency of insulin prescription amongst healthcare providers. Thus, this study is aimed to assess the belief of non-insulin-treated type 2 diabetes patients on insulin prescription and/or therapy.

Methods

Patients' recruitment and study protocol

This is a cross-sectional survey targeting all type 2 diabetes patients attending 15 Primary Care Lifestyle Disease Clinics in Trinidad between March and July 2018. In total, we recruited 510 type 2 diabetes patients (346 females, 164 males) from Regional Health Authorities in the North-Central (305 patients), North-West (103 patients) and Eastern Regions (102 patients) of Trinidad. All the patients were registered and regularly attending Primary Care Lifestyle Disease Clinics at the 15 Healthcare Centres (St. Joseph, Arouca, Cumuto, Sangre Grande, Malony, Woodbrook, Manzanilla, St. Helena, Arima, Maraval, Chaguanas, Macoya, Aranguez, Valencia, and El Socorro) in the three Regional Health Authorities. The patients were not currently treated with insulin for the management of their diabetes and all the participants would have had diabetes for at least six (6) years and were able to complete the face-to-face interview process. They were identified during the clinics and were approached for recruitment into the study. The study protocol as well as the aim and objectives of the study were thoroughly explained to each potential participant. Those who voluntarily consented to participate in the study were made to sign the consent forms before completing the questionnaire or face-to-face interview (for those that could not complete the questionnaire) in a private place within the clinic settings. The research questionnaire contained 17 items of relevant research questions structured around patient's demographic bio-data and patient's beliefs. The questions in the questionnaire tool were a modified version of a validated research questionnaire tool previously employed by other authors in similar studies [11, 23]. The questions were written to limit medical jargons and to guarantee homogeneity in the style of the questioning and confidentiality of the interview process. The study questionnaire was administered to all the patients by one of the authors (YS). The study protocol was reviewed and approved by the University of the West Indies Ethics Review Committee.

Statistical analysis

The data was analysed using a familiar statistical software package (Statistical Package for the Social Sciences, SPSS). For purposes of analytical clarity in terms of the correct belief of the patients to the questions posed, we formulated the response options of "Yes", "No" and "Do not Know" into only two options of "Yes" (interpreted as negative belief in some questions) and "No/Don't Know" (interpreted as positive or neutral). The data was analysed based on gender using chi-squared (χ^2) to test for significance. A p value < 0.05 was considered significant on two-tailed testing.

Results

Figure 1 shows the patient recruitment distribution from the three Regional Health Authorities where the studies were conducted. About 60% of the patients were recruited from the North-Central Regional Health Authority (NCRHA). Table 1 shows that the majority of the patients studied were female (67.8%) and were of East Indian descent (60%). Of the 510 patients studied, 42% were taking one or no oral hypoglycemic agents daily, while 58% were taking two or three different diabetes medications daily (Table 1). Whereas an equal proportion (50.2%) of the patients had primary or no formal western education, a significant percentage (76.3%) were

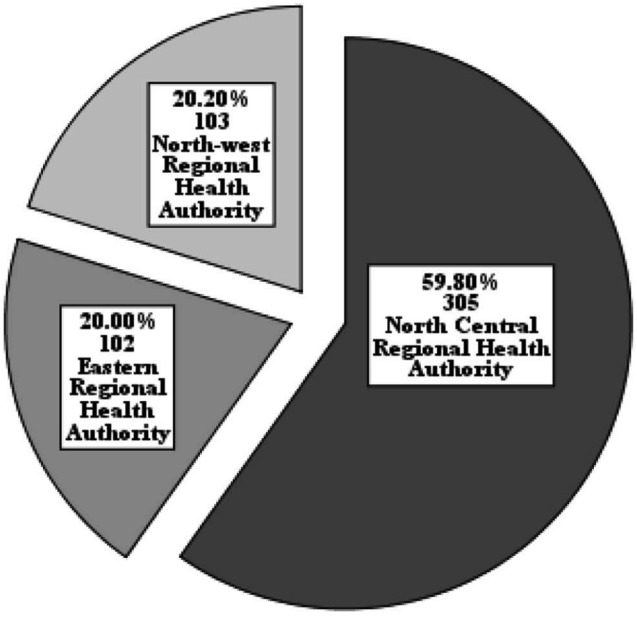

Fig. 1 The distribution of the type 2 diabetes patients recruited from the three Regional Health Authorities in Trinidad

Table 1 Gender-based analysis of the basic demographic characteristics of the patients studied in the three Regional Health Authorities

	All patients ($n = 510$)	Male patients ($n = 164$)	Female patients ($n = 346$)
Racial background			
• East Indian descent, *n* (%)	304 (59.6)	96 (58.5)	208 (60.1)
• African descent, *n* (%)	159 (31.2)	51 (31.1)	108 (31.2)
• Mixed blood, *n* (%)	42 (8.2)	14 (8.5)	28 (8.1)
• Other, *n* (%)	5 (1.0)	3 (1.8)	2 (0.6)
Number of diabetes medications			
• 1 or no medications/day, *n* (%)	214 (42.0)	73 (44.5)	141 (40.9)
• 2 or 3 medications/day, *n* (%)	295 (58.0)	91 (55.5)	204 (59.1)
Levels of formal education: ($p = 0.002$)			
• Primary/no formal education, *n* (%)	256 (50.2)	66 (40.2)	190 (54.9)
• Secondary/tertiary education, *n* (%)	254 (49.8)	98 (59.8)	156 (45.1)
Employment status: ($p = 0.007$)			
• Unemployed/retired, *n* (%)	389 (76.3)	113 (68.9)	276 (79.8)
• Government/self-employed, *n* (%)	121 (23.7)	51 (31.1)	70 (20.2)
Age category			
• < 65 years, *n* (%)	268 (52.5)	85 (51.8)	183 (52.9)
• > 65 years, *n* (%)	242 (47.5)	79 (48.2)	163 (47.1)
Duration of diabetes			
• < 10 years since diagnosis, *n* (%)	223 (43.7)	69 (42.1)	154 (44.5)
• > 10 years since diagnosis, *n* (%)	287 (56.3)	95 (57.9)	192 (55.5)
Average fasting blood glucose/year			
• < 130 mg/dL, *n* (%)	237 (57.0)	76 (55.9)	161 (57.5)
• >130 mg/dL, *n* (%)	179 (43.0)	60 (44.1)	119 (42.5)

retired or unemployed ($p = 0.007$; Table 1). About 47.5% of the patients were older than 65 years (distributed as follows: 25–34 years (2), 35–44 years (29), 45–54 years (68), 55–64 years (169) and 65 years and more (242)). Although a higher percentage (56.3%) of the patients had been living with diabetes for more than 10 years, only 43% reported annual average fasting blood glucose of more than 130 mg/dL (Table 1). In terms of patients' beliefs on insulin therapy or prescription, Table 2 shows that only 33.1% and 18.9% of the patients respectively believe that insulin therapy will cause them hypoglycemia and weight gain. Although higher percentages of the patients believe that taking insulin translates to poor glycemic control (67.6%) or personal failure on optimal blood glucose control (64%), a significant percentage (72.2%) does not believe that taking insulin will interfere with their normal lifestyle activities ($p = 0.048$; Table 2). Similarly, 90% of the patients do not believe that taking insulin will cause people to treat them differently and an equal proportion of the patients (50.6%) thought that if they switch to insulin therapy they would feel better within 6 months (Table 3). Table 3 also shows that a significant majority of the patients did not believe that taking insulin will be helpful in preventing long-term complications (63.9%, $p = 0.001$). Additionally, a significant percentage (81.1%) of the patients do not believe that persons with type 2 diabetes will eventually need insulin therapy for the management of their diabetes ($p = 0.003$; Table 3).

Discussion

This study assessed the beliefs of insulin-naïve type 2 diabetes patients on insulin prescription or therapy, and analysis of our data showed that

1. The majority of the patients studied were female, of East Indian descent, have had diabetes for > 10 years and take multiple oral hypoglycemic agents daily,
2. The majority of the patients do not appear to be deterred by the potential risk of hypoglycemia and weight gain associated with insulin therapy,
3. Whereas the majority of the patients believe that switching to insulin therapy translates to personal failure in optimal blood glucose control, they still believe that insulin therapy will not interfere with their normal lifestyle nor the way people treat them, and
4. Although a significant percentage of the patients do not think that insulin therapy will be helpful in preventing long-term complications, they still believe

Table 2 Gender-based analysis of the responses of the patients to the study questions on insulin therapy or prescription

Responses	All patients ($n = 510$)	Male patients ($n = 164$)	Female patients ($n = 346$)
Do you believe that using insulin will cause your sugar to drop too low?			
• Yes, *n* (%)	168 (33.1)	61 (37.2)	107 (31.1)
• No/do not know, *n* (%)	340 (66.9)	103 (62.8)	237 (68.9)
Do you believe that using insulin will cause weight gain?			
• Yes, *n* (%)	96 (18.9)	27 (16.6)	69 (19.9)
• No/do not know, *n* (%)	413 (81.1)	136 (83.4)	277 (80.1)
Do you believe that taking insulin means that your sugar is uncontrolled?			
• Yes, *n* (%)	345 (67.6)	117 (71.3)	228 (65.9)
• No/do not know, *n* (%)	165 (32.4)	47 (28.7)	118 (34.1)
Do you believe that taking insulin means that you have failed?			
• Yes, *n* (%)	324 (64.0)	107 (66.0)	217 (63.1)
• No/do not know, *n* (%)	182 (36.0)	55 (34.0)	127 (36.9)
Do you believe that taking insulin will interfere with your normal lifestyle? ($p = 0.048$)			
• Yes, *n* (%)	142 (27.8)	55 (33.5)	87 (25.1)
• No/do not know, *n* (%)	368 (72.2)	109 (66.5)	259 (74.9)

that switching to insulin therapy will make them feel better within 6 months.

The above findings are further discussed from the perspective of insulin therapy in developing countries under the following structural subheadings.

Patients demographics, medication and glycemic control

The finding that the majority of the patients studied were females and mainly of East Indian descent was a reflection of the general uptake in the Lifestyle Disease Clinics in this population [1–3]. Female patients tend to be more regular than males in keeping their clinic appointments, and a higher proportion of patients being of East Indian descent is consistent with ethnic proportional prevalence of diabetes in this population [24]. Indeed, because of the high prevalence of diabetes in this population [24], and it has been increasing, it is not unexpected that a higher percentage would have been living with the condition for > 10 years. The finding that 58% of the patients take more than two different diabetes medications daily is an indication of poor glycemic control amongst the type 2 diabetes patients studied. We have previously reported

Table 3 Gender-based analysis of the responses of the patients to the study questions on insulin therapy or prescription

Responses	All patients ($n = 510$)	Male patients ($n = 164$)	Female patients ($n = 346$)
Do you believe that by taking insulin it will cause people to treat you differently?			
• Yes, *n* (%)	53 (10.4)	20 (12.3)	33 (9.6)
• No/do not know, *n* (%)	455 (89.6)	143 (87.7)	312 (90.4)
If your doctor switches you to insulin therapy, do you think that in 6 months it will make you feel better?			
• Yes, *n* (%)	257 (50.6)	81 (49.7)	176 (51.0)
• No/do not know, *n* (%)	251 (49.4)	82 (50.3)	169 (49.0)
Do you believe that taking insulin leads to good long-term outcomes such as living longer? ($p = 0.001$)			
• Yes, *n* (%)	182 (35.8)	75 (45.7)	107 (31.0)
• No/do not know, *n* (%)	327 (64.2)	89 (54.3)	238 (69.0)
Do you believe that taking insulin leads to good long-term outcomes such as preventing further problems? ($p = 0.001$)			
• Yes, *n* (%)	183 (36.1)	77 (47.5)	106 (30.7)
• No/do not know, *n* (%)	324 (63.9)	85 (52.5)	239 (69.3)
Do you believe that all persons with type 2 diabetes will eventually need to take insulin? ($p = 0.003$)			
• Yes, *n* (%)	96 (18.9)	43 (26.2)	53 (15.4)
• No/do not know, *n* (%)	413 (81.1)	121 (73.8)	292 (84.6)

on high prevalence of poor glycemic control and the risk of developing coronary heart disease (CHD) amongst type 2 diabetes within 10 years [25–27].

Beliefs on hypoglycemia and weight gain associated with insulin therapy

The finding that the patients studied do not have a significant negative opinion regarding hypoglycemia and weight gain associated with insulin therapy is not consistent with previous reports [12–19]. Indeed, the risk of hypoglycemia amongst patients on insulin therapy is real and well-documented and could result from wrong insulin titration, over dosage or skipping meal before or after insulin injection [28, 29]. Patients newly switched to insulin therapy must undergo structured diabetes education on insulin therapy particularly as related to insulin titration, self-injection of insulin and signs of severe hypoglycemia [28, 29]. It is almost commonsensical that patients with sufficient knowledge of these potential risks of insulin therapy would have a negative perception that would require proper diabetes health education for them to accept the therapy. For instance, it is likely that many patients would prefer the option of different oral hypoglycemic agents in place of insulin therapy as seen in this study where 58% of the patients were on different oral hypoglycemic agents (Table 1). The issue of weight gain is also one of the myths and misconceptions about insulin therapy in type 2 diabetes patients [29]. A previous study has shown that patients on insulin therapy intentionally skipped insulin dose because of fear of gaining weight [30]. We are not certain if the responses of the patients in this study were based on lack of knowledge of the true risks associated with insulin therapy or a true reflection of a positive reception of a potential treatment option available for optimal management of their diabetes. Perhaps, further studies are warranted to interrogate this finding.

Belief on switch to insulin therapy as a personal failure in glycemic control

The finding in this study that the patients studied would consider a switch to insulin therapy as a sign of personal failure to control blood glucose level is consistent with reports of the myths and misconception of insulin therapy [29, 31]. Indeed, some authors have also attributed the patients' perceived failure to the patients' personal experiences which included, amongst others, perceived loss of control over one's life and injection-related anxiety [19]. The patients' belief that uncontrolled blood glucose level is a personal failure may well be so given that many healthcare providers, especially in the developing countries, consider a switch to insulin therapy as a treatment of last resort because of several barriers associated with insulin treatment [20, 31]. Thus, most patients nurture the feeling that insulin therapy is a punishment for their failure to control their blood glucose level. It is of interest that the patients studied are favourably disposed to insulin therapy as a treatment option. Furthermore, contrary to previous negative perception report [31, 32], the patients studied do not believe that the society will treat them differently nor will the treatment affect their normal life activities. This finding may be related to both cultural perspective of the study population and healthcare system in the developing countries. In this population, and perhaps in most developing countries, patients do trust their healthcare providers in terms of their medical decisions to the extent that seeking second medical opinion is almost minimal. This may be associated with the literacy levels in most developing countries; for instance, in this study, 50% of the patients had primary or no formal western education (Table 1). Although there is no difference between literate and non-literate patients in terms of adherence to medications [20], secondary and/or tertiary education may be important in understanding the many intricacies involved in medical decisions.

Belief on insulin therapy and diabetes long-term complications

The finding that the majority of the patients do not think that insulin therapy will assist in preventing long-term diabetes complications is a demonstration of inadequate diabetes education on the causes of micro- and macro-vascular complications in type 2 diabetes patients [33]. This particular finding is rather paradoxical given that the same group of respondents believe that a switch to insulin therapy would make patients feel better within 6 months (Table 3). This, perhaps, is the consequence of inadequate diabetes health education warranting a call for intensification of diabetes self-management education in the developing countries [34]. It is likely that patients attending more sophisticated Lifestyle Disease Clinics would know that the intention for insulin therapy is to tighten glycemic control, reduce HbA_{1c} levels and consequently reduce micro- and macro-vascular complications often prevalent in uncontrolled type 2 diabetes patients [33]. We believe that diabetes patients in this population will benefit from the newly developed diabetes health education tool that addressed the myths, misconceptions and clinical realities of insulin therapy [31].

Limitations of the study

We advise for caution in the interpretation and use of the result from this study given some observed limitations.

First, there is an unintended skewed sample size towards one racial group (East Indian descent) comprising about 60% of the patients studied. It is possible this might have introduced skewed ethnic opinion which may not reflect the opinion of the general diabetes population in this country. Trinidad and Tobago is a multi-ethnic, multi-cultural society with two major ethnicities of African descent (40.0%) and East Indian descent (40.3%) [35]. Thus, we caution that until the study is extended to Tobago Island with high population of people of African descent, the findings here can only serve as a preliminary study. Furthermore, the study was conducted at the primary care settings with limited diabetes health education infrastructure; it is possible that patients attending secondary and tertiary Lifestyle Disease Clinics might have different beliefs and opinions. These limitations notwithstanding, the study has documented, for the first time in the Caribbean population, the beliefs of type 2 diabetes patients on insulin therapy or prescription.

Conclusions from the study

We believe that this report could serve as a template for further studies in other Caribbean countries. Until further studies are conducted, we conclude that contrary to several reports [12–19], insulin-naïve type 2 diabetes patients in this population do not have significant negative opinion towards insulin therapy or prescription. This finding might be related to the general socio-cultural background of the patients studied.

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Authors' contributions CEE: contributed in the concept, design, data analysis, data acquisition, statistical analysis, manuscript preparation and writing

PO: design, data analysis, data acquisition, manuscript preparation and review

SY: design, data acquisition, statistical analysis, manuscript preparation and review

RE: design, data analysis, statistical analysis, manuscript preparation and review

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

The effect of metabolic control, self-efficacy, and quality of life on emotional eating in the adolescents with type 1 diabetes mellitus

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Abstract

Purpose The purpose was to investigate the effects of metabolic control, self-efficacy, and quality of life on emotional eating in the adolescents with type 1 diabetes mellitus.

Methods This was a descriptive, cross-sectional, and correlational study. A total of 107 adolescents participated. Data were collected using the Pediatric Quality of Life Inventory™ 3.0 Diabetes Module, the Diabetes Management Self-Efficacy Scale, and the Emotional Eating Scale. The relationships among emotional eating, metabolic control, self-efficacy, and quality of life were assessed using bivariate correlation analyses. Multiple regression analysis was used to analyze the data.

Results The adolescents with diabetes ranged in age from 11 to 18 years. The mean duration of diabetes was 5.42 ± 3.35 years. Mean A1C levels were 9.29 ± 1.38%, far above the recommended level. When the correlation between emotional eating and self-efficacy was studied in the adolescents, there was a significant positive moderate correlation of self-efficacy with emotional eating. There was a significant negative moderate correlation between quality of life and emotional eating, but no significant correlation between A1C and emotional eating.

Conclusion As a result of the study, it was found that self-efficacy and quality of life of adolescents with type 1 diabetes have an effect on emotional eating, while A1C values of adolescents have no effect on emotional eating. In future studies, it is recommended to add other factors that may affect the emotional eating behaviors of adolescents with diabetes and also to make different studies with a higher number of samples.

Keywords Type 1 diabetes mellitus · Self-efficacy · Quality of life · Emotional eating

Introduction

Nutritional management is one of the cornerstones of diabetes care and education in adolescents with type 1 diabetes mellitus (T1DM). The International Society of Pediatric and Adolescent Diabetes' Guidelines [1] noted that nutritional therapy is critical and eating problems are common, especially in adolescence when challenging behaviors may include staying out late, sleeping in, skipping insulin, missing meals, and, in some cultures, drinking alcohol [1]. Healthy nutrition is very important for improving T1DM outcomes and to minimize the advent of complications.

Adolescence is a period in which children with diabetes transition to managing their diabetes and food intake more independently of their families. In this period, adolescent's behavior patterns change, leading them to take risky actions (e.g., getting up late, skipping meals), and they meet friends and go to parties without telling their families. Preventing eating problems is a goal of nutritional care of adolescents with T1DM [1]. Previous research has supported that the prevalence of eating problems in adolescents with T1DM is twice that of those without diabetes and that eating problems are more common in girls than boys with T1DM [2]. Many adolescents may experience a deterioration in metabolic control [2], often attributable to erratic meals, poor adherence to treatment regimens, hazardous and risk-taking behaviors,

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disordered eating behaviors, and the natural insulin resistance associated with puberty [3, 4].

Recently, emotional eating (EE) has been found to be common especially in adolescents. EE is defined as changing eating habits in response to negative situations and emotions and using food to cope with stress. Understanding the causes of these behaviors in adolescents is very important to prevent further eating problems [5]. Previous studies have shown that emotions are among the important factors that determine eating behaviors and food choices. In EE, nutrients are used to control the emotional state, and these nutrients are often high-fat and sweet and high-energy foods [6]. Adolescents with EE eat more high-calorie foods compared with adolescents without these problems. Adolescents consume these nutrients as a method of coping with negative mood, and girls often consume high-calorie and sugary foods in stressful situations [6, 7]. Studies on EE showed that girls consume too much food not only in cases of negative mood but also in positive mood [8]. Eating in response to negative emotions is likely to persist throughout life and negatively impact one's health. There are some studies showing that A1C, self-efficacy, and quality of life affect the eating behaviors of adolescents with T1DM [9].

The results of the Diabetes Control and Complications Trial (DCCT) show that, among patients undergoing intensive glycemic control, consumption of low-carbohydrate, high-fat (particularly high-saturated fat) diets is associated with poorer metabolic control [10]. Among adolescents with T1D, irregular or infrequent meal consumption appears being associated with poorer metabolic control. Routinely assessing eating patterns in adolescents with T1DM is too important for improved metabolic control [11].

Having high self-efficacy for nutrition is particularly effective on developing positive nutrition behaviors. High self-efficacy is also effective in the development of positive behavioral change for healthy food choices. In Fitzgerald et al. study [9] on 483 adolescents 13–18 years old, those with higher self-efficacy consumed healthier foods, while those with lower self-efficacy consumed unhealthier foods. In addition, those with higher quality of life and mood had better eating habits. Promoting positive health behaviors plays a key role in maintaining health and metabolic control of diabetes. This understanding is based on the notion that achieving behaviors sustain and improve health status and make the positive decisions about individual health [12]. Kumcağız et al. [13] reported significant associations between quality of life and eating behaviors of adolescents. There have been few studies that have investigated metabolic control, self-efficacy, and quality of life in adolescents with type 1 diabetes and EE problems [14, 15]. Thus, the aim of this study was to examine the relationship of metabolic control, self-efficacy, and quality of life on EE in adolescents with T1DM.

Research questions

Our research questions were:

- Q_1: What is the relationship between *self-efficacy for diabetes self-management scores* and mean eating scores of adolescents with T1DM?
- Q_2: What is the relationship between *quality of life scores* and mean eating scores of adolescents with T1DM?
- Q_3 What is the relationship among *A1C levels*, *self-efficacy diabetes self-management*, *quality of life scores*, and mean eating scores of adolescents with T1DM?

Methods

Participants

This was a descriptive, cross-sectional, and correlational study designed to examine the relationships among A1C, self-efficacy, quality of life, and EE on adolescents with T1DM. We used G*Power 3.0 statistics software to determine sample size using the parameters effect size of 0.5, type 1 error as 0.01, and type 2 error as 0.01 (99% power) and using the regression analysis which resulted in a required sample size of 77 adolescents. Ultimately, 107 adolescents with T1DM had parents who gave permission for their participation, volunteered for the study and completed the questionnaires without leaving any questions blank. The inclusion criteria were T1DM diagnosed at least a year before enrollment and age 11–18 years of age. The exclusion criteria were the presence of thyroiditis or celiac disease, both of which are often concomitant with diabetes, and/or the presence of either diabetes-related or unrelated neurologic problems.

Measures

Data were collected using a demographic data form (e.g., age, sex, parents' educational status, years with diabetes), the Pediatric Quality of Life Inventory™ 3.0 Diabetes Module, the Turkish version of the Diabetes Management Self-Efficacy Scale in Adolescents with Type 1 Diabetes Mellitus, and the Turkish version of the Emotional Eating (EE) Scale.

Pediatric Quality of Life Inventory™ 3.0 Diabetes Module—Turkish form

This scale was developed originally by Varni et al. [16] and adapted for Turkish use by Ayar and Oztürk [17]. The Cronbach alpha for the Turkish version of the scale was 0.86. The Kaiser–Meyer–Olkin (KMO) coefficient was found

to be 0.80 and $\chi 2 = 15.275$ ($p < 0.001$), respectively. A five-point Likert scale was used in which 0 = never a problem and 4 = almost always a problem. Items were linearly transformed to a 0–100 score. The score was 100 if the items were rated "never a problem" and 0 if the items were rated "almost always a problem." Thus, higher scores indicate higher health-related quality of life. This scale is a reliable and valid instrument that can be used by diabetes teams to measure the quality of life in Turkish children with T1DM [17].

Diabetes Management Self-Efficacy Scale in Adolescents with Type 1 Diabetes Mellitus

This scale was developed originally by Moens [18], and its Turkish validity and reliability was determined by Ozturk et al. [19]. The scale includes 26 single-choice items scored on a 5-point scale ranging from 1 (definitely yes) to 5 (definitely not). Self-efficacy scores are summed and divided by the total number of items to indicate the strength of perceived self-efficacy for performing various diabetes self-management activities. *High scores represent lower self-efficacy*. The total Cronbach's alpha internal consistency reliability coefficient value was 0.85. This scale is a disease-specific instrument for evaluating self-efficacy in Turkish adolescents with T1DM [19].

Turkish version of the emotional eating scale

This scale was developed to determine EE status of children and adolescents between the ages of 8–17 years. The original adult scale was adapted by Tanofsky-Kraff et al. [20] for American children and adolescents. The scale is composed of 25 items about emotional status-related eating behaviors. Validity and reliability assessment of the Turkish version was conducted by Bektas et al. [21]. The KMO coefficient was 0.904, and the Bartlett test result was $\chi^2 = 5630.693$ ($p < 0.001$). The total Cronbach's alpha coefficient was 0.90. Thus, this scale has high validity and reliability for the Turkish samples [21].

Data analyses

SPSS Software, version 22.0, was used for all statistical analyses. Descriptive analyses were conducted using percentages, means, and standard deviation. The relationships among EE, metabolic control, self-efficacy, and quality of life were assessed using bivariate correlation analyses (Pearson's r). The Pearson correlation coefficient is a bivariate statistics that measures how strongly two variables are related to one another. Effects of adolescents' metabolic control, self-efficacy, and quality of life level on their emotional eating level were assessed using multiple linear regression analyses. Multiple variables were used to determine whether these variables would be included in the model. Multiple correlation tests are required to have a VIF of less than 10, a tolerance value of more than 0.2, and a condition index of less than 15. Variables in this study are included in the model as they meet the desired criteria.

Results

The adolescents with T1DM ranged in age from 11 to 18 years (mean, 13.97 years; SD, 1.87 years). The mean duration of diabetes was 5.42 ± 3.35 years. Their mothers were high school graduates (33.6%), and 39.3% of their fathers (n = 42) were university graduates. Adolescents did not count carbohydrates (55.1%, $n = 59$). Mean A1C levels were 9.29 ± 1.38%, far above the recommended level.

When the correlation between EE and self-efficacy was studied in the adolescents, there was a significant positive moderate correlation of self-efficacy with EE ($r = 0.576$, $p < 0.001$). There was a significant negative moderate correlation between quality of life and EE ($r = -0.577$, $p < 0.001$), but no significant correlation between A1C and EE ($r = -0.004$, $p > 0.001$) (Table 1).

The multiple regression analysis in model 1 found that there was a moderately significant positive relationship between EE and self-efficacy levels of the adolescents ($\beta = 0.576$, $p < 0.001$) and 33% of the factors affecting EE were accounted by the mean total score of the self-efficacy ($F = 52.201$). It was determined in model 2 that there was a moderately significant negative relationship between EE and quality of life ($\beta = -0.577$, $p < 0.001$) and 33% of the factors affecting EE were accounted by the mean total score of the quality of life ($F = 52.498$, $p < 0.001$). When the relationship between adolescent EE levels and other variables was examined in model 3, a significant negative relationship at a moderate level was found between EE and quality of life levels ($\beta = -0.408$, $p < 0.001$), and there was no relationship between EE and A1C level ($\beta = -0.034$, $p > 0.001$). EE levels

Table 1 The relation of adolescent with type 1 diabetes mellitus' emotional eating with their self-efficacy and quality of life

	Emotional eating	Self-efficacy	Quality of life
	r	*r*	*r*
Emotional eating	1.0*		
Self-efficacy[a]	0.576*	1.0*	
Quality of Life	− 0.577*	− 407*	1.0*
A1C	− 0.004**		

*The correlations significant at $p < 0.001$

**$p > 0.001$

[a] High scores represent less self-efficacy

had a moderately significant positive relationship with self-efficacy levels ($\beta = 0.414$, $p < 0.001$). It was determined that EE levels were affected most by self-efficacy, quality of life, and A1C variables, respectively. Overall, 47% of the factors that affect EE levels were explained by self-efficacy, quality of life, and A1C variables ($F = 28.175$, $p < 0.001$) (Table 2).

Discussion

The results of this study demonstrate the relationships of A1C, self-efficacy, and quality of life with EE of adolescents with T1DM. In the literature, it has long been emphasized that the low quality of life and self-efficacy of adolescent with diabetes affect metabolic control and that these changes in metabolic control give rise to a change in emotional state. Adolescents have mostly reported that eating behavior is often resorted to cope with changes in mood. In the light of this information, a model was created in this study. Three models were created to consider the correlations between variables. Model 1 examined the relationship between self-efficacy levels and mean EE scores. Model 2 examined the relationship between quality of life and mean EE scores. Model 3 examined the relationship between EE levels and the mean scores of all other variables (self-efficacy, quality of life, and A1C).

Monitoring and managing food intake are integral to the management of T1DM. Dietary advice given to adolescents with T1DM is based on principles of healthy eating principles. Adherence to dietary advice is often reported as one of the most difficult aspects of diabetes management, and this difficulty has potential impacts on the emotional aspects of eating [22]. Youth may experience challenges, and these may affect diet and meal planning, as their school, activity, and social schedules become more variable, and they have more responsibility for food choices away from home [23]. There are many factors that may be related to food choice and eating patterns of adolescents with diabetes mellitus. One of the factors that may affect food choice is EE. EE has been linked to higher consumption of unhealthy foods (e.g., foods high in fat, sugar, and salt) [24] and negative nutritional outcomes [25]. Kemp and Grier [24] identified significant outcomes of EE, including decreased motivation to process nutritional information and overconsumption. Those with EE behaviors are prone to consuming and sometimes overconsuming unhealthy foods, when experiencing negative and positive emotional states.

Table 2 Multiple linear regression analysis of the factors that affect emotional eating

	Model 1	Model 2	Model 3
	β	β	β
Self-efficacy	0.576		0.414
Quality of life		− 0.577	− 0.408
A1C			− 034
R^2	0.332	0.333	0.468
F	52.201	52.498	28.175
p	< 0.001	< 0.001	< 0.001

*$p < 001$

Model 1 showed that adolescents with high self-efficacy levels also had high EE levels. In this study, self-efficacy level occupies an important place among the factors that affect EE level (33%, Table 2). Adolescents with a high level of self-efficacy had 0.57 times higher EE levels. High self-efficacy for a behavior is important to making behavioral changes. Enhanced diabetes self-efficacy has been linked to improved glycemic control and is an important indicator of health behavior changes in youth. Previous studies have shown that self-efficacy is very important for developing and maintaining healthy eating behaviors in adolescents (e.g., consumption of fruits and vegetables, avoiding high-energy foods) [26]. Pinhas-Hamiel et al. [27] found that lower T1DM regimen adherence is associated with lower self-efficacy in adolescents. Survonen et al. [28] found a positive association between self-efficacy and understanding of diabetes and its treatment, adjustment to diabetes, and dietary adherence in adolescents with diabetes. The literature supports the result that adolescents with low self-efficacy levels also have high levels of EE.

In this study, a moderate significant negative association was observed between quality of life and EE behaviors in adolescents with T1DM. Model 2 showed that adolescents with high quality of life levels also had low EE levels. There are studies showing the direct effects of quality of life on the EE behaviors and an association between EE behaviors and quality of life in the adolescents. In the literature, there are few studies in which the association of quality of life and EE status was studied. Some of these studies showed a negative significant association between eating disorders and quality of life especially in obese children, and health-related quality of life of people with eating disorders was low as compared with those without such disorders [15]. The quality of life of adolescents with diabetes affects not only EE but also self-efficacy level [14, 29]. Therefore, the effect of all variables on emotional eating should be examined together.

Model 3 showed that adolescents with high mean scores for self-efficacy and low quality of life had high emotional eating level. In this study, these three variables together occupied an important place among the factors that affect emotional eating level (47%). Emotional eating is defined as a tendency to overeat in response to negative emotions. A tendency to positive and negative emotion states is observed in emotional eating behavior. In other words, eating behavior is affected by emotions. Emotional

eating is when an individual tends to consume excessive, high calorie, and non-nutritious foods. It is stated that eating salty, oily, and sweet foods may cause excess weight gain. Individuals who consume such food do not consider the things that affect their mood [5, 6, 7, 8]. However, this is a temporary situation. People with emotional eating problems experience concern about their weight control and health after this behavior, and emotional eating behavior is triggered, and after a while, it turns into a vicious circle. This is very risky for diabetes management. Dietary compliance of adolescents with diabetes is one of the important building blocks of the management of the disease, and diabetic adolescents' compliance with the amount of carbohydrate intake given by the diabetes team is directly related to glycemic control. Therefore, although there is no significant relationship in this study, it is thought that A1C levels may be affected in the later periods, as the emotional eating status of adolescents with diabetes will affect food intake. Contrary to the results of this study in literature, poor adherence to diet was strongly associated with elevated A1C levels. Reinehr et al. [30] reported that worsening of A1C levels was associated with specific eating problems in girls with T1DM.

Conclusion and recommendations

In this study, the A1C values of the adolescents were above the target value ranges (International Society of Pediatric and Adolescent Diabetes guidelines), so the relationship between the A1C value and the EE principle could not be determined clearly. It is recommended to highlight this issue during the education of the adolescents with T1DM in the future studies and to monitor the EE status of the adolescents regularly in the clinic.

As a result of the study, it was found that self-efficacy and quality of life of adolescents with type 1 diabetes have an effect on emotional eating, while A1C values of adolescents have no effect on emotional eating. In the literature, there are no studies examining the effects of self-efficacy, quality of life, and A1C levels on emotional eating together in adolescents with diabetes. Therefore, our study would contribute to the field. In this study, it is suggested that the self-efficacy levels of adolescents should be determined regularly and training programs should be established to increase self-efficacy, and at the same time the quality of life levels should be monitored regularly. In future studies, it is recommended to add other factors that may affect the emotional eating behaviors of adolescents with diabetes, also to make different studies with a higher number of samples, and to create training programs for those with a tendency to eat emotionally.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Permission was obtained via email from the owners of the scales used in the research. The written consent of University Non-Invasive Research Ethics Board (3523-GOA: 2017/21-14) and also permission from the institution itself was received.

Informed consent Before the study was conducted, adolescents and their parents were informed of the purpose of the research, and written permission was obtained from the adolescents and parents who agreed to participate.

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CASE REPORT

Frameshift variance in SLC19A2 gene causing thiamine responsive megaloblastic anemia (TRMA): a case report from Pakistan

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Abstract

Background Thiamine responsive megaloblastic anemia syndrome is a rare genetic disorder usually associated with sensorineural deafness, megaloblastic anemia, and/or diabetes mellitus due to mutations in SLC19A2, encoding a thiamine transporter protein.

Case report In this case, we report a 2.5-year-old baby boy born to consanguineous parents. He was noted to be deaf and mute during his first year of life. He was diagnosed with anemia at the age of 15 months and required blood transfusion twice. The cause of anemia was not established and it was attributed secondary to some viral infection. At the age of 2 years, he was diagnosed with DM. The diagnosis of TRMA had been made during his evaluations for uncontrolled blood glucose, sensorineural deafness, and anemia. After few weeks of thiamine replacement, his hemoglobin increased to normal values; his sugars improved but had no changes in his deafness.

Methods Analysis of all coding regions and exon/intron boundaries of the SLC19A2 gene by Sanger sequencing.

Results A p,Leu208fs homozygous frame shift variant is identified in the SLC19A2 gene, located on the Exon 2 and DNA description is c.623dup. This variant is predicted to be pathogenic and diagnosis of TRMA syndrome is confirmed.

Conclusion The diagnosis of TRMA should be kept in mind in differential diagnosis of DM with anemia and or sensorineural hearing loss. Particularly in the populations where the consanguinity is frequent as diagnosis has great impact on management.

Keywords Thiamine deficiency · DM · Sensorineural hearing loss · Megaloblastic anemia · SLC19A2 gene

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Introduction

Thiamine responsive megaloblastic anemia (TRMA) syndrome or Roger's syndrome is a rare genetic disorder that follows autosomal recessive pattern. It is usually associated with sensorineural deafness, megaloblastic anemia, and variable onset monogenic diabetes mellitus [1]. Additionally, abnormalities of cardiovascular system like congenital heart diseases, cardiomyopathy, arrhythmias, stroke, and disorders of retina and optic nerve [2] as well as thrombocytopenia and pancytopenia are reported in association with TRMA syndrome [3, 4].

This syndrome occurs due to mutations in SLC19A2 gene, located on the long arm of chromosome 1 [2, 5], encoding a thiamine transporter protein in bone marrow, pancreatic beta cells, and a subset of cochlear cells. The active uptake of thiamine into the cells is disturbed in this disorder leading to defects in cellular metabolism, cell stress, and apoptosis [2].

Here, we report a case with TRMA syndrome to describe clinical features of this rare entity and useful effects of thiamine on predominantly hematologic parameters.

Case report

A 2.5-year-old baby boy attended outpatient department of Baqai Institute of Diabetology and Endocrinology with high glucose levels. He was the first child of healthy consanguineous (first cousin) parents. He was born full term, with a birth weight of approximately 2.75 kg, through normal vaginal delivery. He was noted to be deaf and mute during his first year of life.

He was diagnosed with anemia at the age of 15 months and required blood transfusion twice. The cause of anemia was not established and it was attributed secondary to some viral infection. At the age of 2 years, he was diagnosed with DM and he was taking insulin (basal bolus regimen) but his glucose level was not controlled.

During physical examination, the child's look was normal and had no dysmorphic features. However, he had moderate pallor with no associated signs of jaundice or cyanosis. His vital signs were within the normal range, both his weight and height were in the 75th percentile. Systemic examinations including cardiac and ophthalmologic examinations were normal and hearing loss was detected.

Lab findings at the time of presentation are as follows. HbA1c 10.9%, fasting blood glucose 200 mg/dl, and random blood glucose was 320 mg/dl. Hemoglobin was 7.7 g/dl, MCV 96 fl with normal leucocytes and platelet count. A peripheral blood film showed macrocytic, hypochromic anemia with anisocytosis, polychromasia, and poikilocytosis. Vitamin B_{12}, iron, and folate levels were normal. Similarly, urea, creatinine, and electrolytes were within normal range. Urinalysis was negative for ketone and protein. Autoantibodies for pancreatic beta cells were negative.

Bone marrow examination was planned but parents did not give consent for aspiration. The brainstem evoked response audiometry was subsequently performed and severe bilateral sensorineural hearing loss was detected. Because of financial constraints, cochlear implant was not done. Hearing aids were therefore offered to the patient.

Considering his uncontrolled blood glucose, sensorineural deafness, and recurrent anemia, the diagnosis of TRMA had been suspected. Sequencing analysis of all coding regions and exon/intron boundaries of the SLC19A2 gene was done. A p, Leu208fs homozygous frame shift variant was identified. It was located on the Exon 2 and DNA description was c.623dup. This variant was predicted to be pathogenic and diagnosis of TRMA syndrome was confirmed. Thiamine at the dose of 100 mg/day was started. On next follow-up, within few weeks of thiamine replacement, his hemoglobin increased to normal values; his glucose level improved but had no changes in his deafness.

Discussion

We present a case of novel mutation (frameshift variance) of SLC19A2 in a baby boy with TRMA syndrome, a rare autosomal recessive disorder with a high prevalence among consanguineous families.

Thiamine deficiency may lead to selective loss of inner hair cells of the cochlea resulting in irreversible sensorineural hearing loss that is progressive and unresponsive to thiamine treatment [6]. In our case, hearing loss was detected within 1 year of life and it was not improved with thiamine treatment. On the contrary, Önal et al. reported a case who had no hearing loss at diagnosis and did not develop afterwards [7].

Megaloblastic anemia typically begins in early childhood [2]. Beshlawi et al. [8] stated that hematological response to thiamine was variable, anemia improves, but mean corpuscular volume remained high throughout life. Suspension of treatment consequently leads to recurrence of anemia. Additionally, dur-

Table 1 Gene characteristics, description, and remarks

Characteristics	Description	Remarks
Gene name	*SLC19A2*	
Gene structure	*SLC19A2* spans approximately 22.5 kb	Six exons with a 237-bp 5' UTR and a 1620-bp 3' UTR
Chromosome	1q23.3	
Exon	1-6	Most common mutation is on exon 2; however, mutation on exon 1, 3, and 4 are also identified
Locus protein	Thiamine transporter 1	
Pathogenic variant	Intragenic deletions/insertions/missense/nonsense and splice site variants	More than 40 families with 33 distinct pathogenic variants have been identified
Test methods	Quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA)	A gene-targeted microarray designed to detect single-exon deletions or duplications is also available in some centers
Pattern of inheritance	Autosomal recessive	Homozygosity has been the most common finding although seven individuals from six families were found compound heterozygous

ing treatment, unresponsiveness to thiamine may develop [9]. Our case responded to thiamine adequately and his hemoglobin improved to normal level.

Autoantibodies that are characteristic of type 1 diabetes are negative and prime defect is in insulin release. In fewer cases, it was found that insulin requirements reduced with the thiamine treatment [2, 3, 8] as was the case in our patient, his insulin dose was needed to be decreased and his glycemic control improved within a few weeks of thiamine treatment. Similarly, some studies noted that majority of cases become insulin-dependent by the time they reach puberty [9].

Similarity exists between TRMA and Wolfram syndrome (DIDMOAD) including DM, optic atrophy, and deafness but notably missing is megaloblastic anemia and responsiveness to thiamine. Pathogenic variants are WFS1 that cause Wolfram syndrome. Moreover, combination of DM and sensorineural hearing loss put mitochondrial disorders as an important differential but the macrocytic anemia and responsiveness to thiamine distinguish TRMA from these disorders [9]. Furthermore, inheritance in TRMA is autosomal recessive, while in mitochondrial disorders, it follows mitochondrial inheritance pattern.

Mutations in the *SLC19A2* gene with six exons that reside on chromosome 1q23.3 cause TRMA syndrome. Though most common mutations are found in exon 2, mutations in the exons 1, 3, and 4 are also identified [10]. In our patient, sequencing analysis of the *SLC19A2* gene identified a p, Leu208fs homozygous frame shift variant that was located on the Exon 2 (Table 1).

Conclusion

The diagnosis of TRMA syndrome should be kept in mind in differential diagnosis of DM with anemia and or sensorineural hearing loss. Particularly in the populations where the consanguinity is frequent as diagnosis has great impact on management. Moreover, genetic counseling should also be provided.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was taken from participant.

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LETTER TO THE EDITOR

Understanding goals and challenges in type 2 diabetes mellitus management in India: Time to do more in diabetes

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Despite the availability of a plethora of well-tolerated treatment options, optimal therapeutic glycemic targets are not met in almost half of the people with diabetes [1–3]. A nationwide, cross-sectional survey in India was conducted in lines with a global survey by market research company, Kantar Health across 6 countries [4]. The objective was to gain clarity in the attitudes, behaviors of physicians, and patients towards diabetes management, identify underlying factors for clinical inertia, and seek solutions to improve management.

For a period of 2 months, the respondents (diabetes patients aged 40–69 years and physicians) were interviewed face-to-face across twenty-five tier I and tier II cities divided into five geographic zones. The healthcare professionals were selected through random sampling. Participant's consent regarding confidentiality, adverse event reporting, non-promotional exercise, was obtained prior to the survey. The questionnaire covered 3 main aspects—diagnosis consultation, hypoglycemia awareness and reporting, and getting to glycemic goals. The final sample achieved post corroboration to the screening criteria was 638 for physicians and 641 for type 2 diabetes patients.

There is an evident gap in communication between physicians and patients. Key topics on drug treatment, lifestyle changes, blood sugar control, and monitoring were discussed extensively in consultation by physicians. However, patients' understanding remained modest (51%) (Fig. 1). Patient recollection of topics discussed was poor, which suggests communication gaps. Approximately, one (22%) in five patients reported hypoglycemia. Only 40% physicians felt that hypoglycemia is under-reported. Eighty-four percent patients who reported hypoglycemia were briefed during consultation. Thus, if patients are sensitized to hypoglycemia, they are more likely to report it.

There is strong need to facilitate commitment to lifestyle and dietary modifications, and compliance to medications among patients. In our study, there was a gap in physicians feeling and patient reality with regard to compliance. While 72% patients said that they were compliant to medications, according to physicians, only around 40% patients of all profile were likely to comply. The difference could be because patients may relate compliance with medication, but physicians relate it with both medications and lifestyle changes. Patients finding it difficult to make dietary changes, and adapt to exercise habits were cited by 40% of physicians as two primary reasons which deter patients from reaching their glycemic goals.

Due attention to diagnosis consultation, hypoglycemia reporting and steps to getting the HbA1c to goal will require understanding and an alliance between physicians and patients to improve diabetes care.

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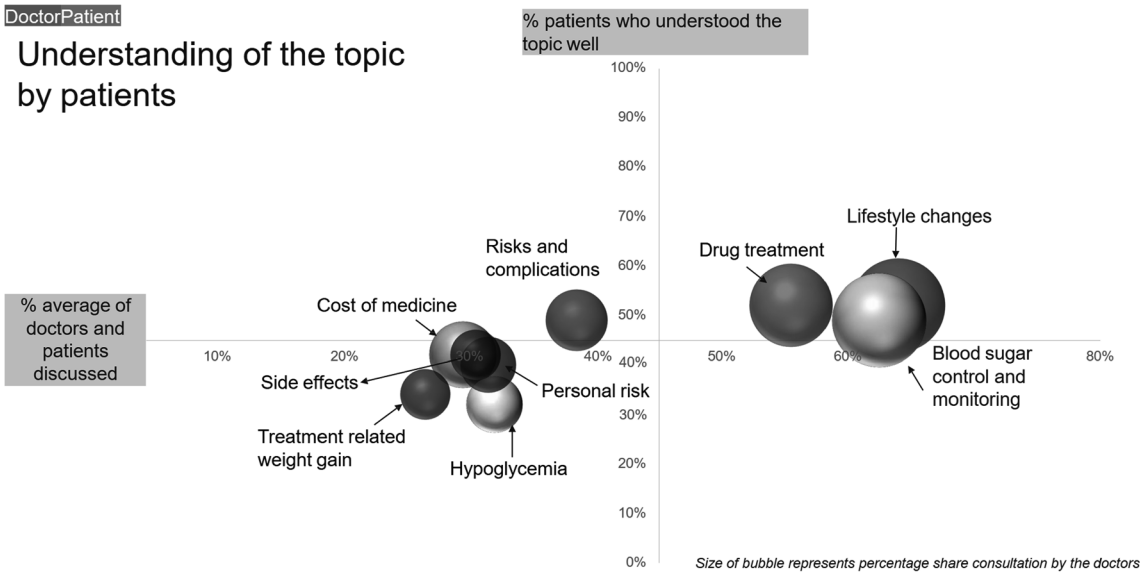

Fig. 1 Understanding of topics by patients versus topics discussed

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Contributors All contributors were part of National Steering Committee Meeting wherein deliberations related to questionnaire, overall conduct, and analysis of the results were done. All contributors represented the different geographic zones where they chaired regional steering committee meetings.

Prior presentation Part of the data presented at the following conferences-

Endocrine Society of India 48th Annual conference, Scientific Programme - ESICON 2018. Indian J Endocr Metab 2018;22, Suppl S1:6–13, Bhubaneshwar, November 2018.

Mithal A et al. Poster presentation. 55th EASD Annual Meeting of the European Association for the Study of Diabetes: Barcelona, Spain, 16 - 20 September 2019. Diabetologia. 2019 Sep;62(Suppl 1):1-600.

Dharmalingam M et al. Poster presentation. International Diabetes Federation Congress 2019 (BU-04360) : Busan, South Korea, 02 - 06 December 2019.

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Compliance with ethical standards

Conflict of interest The study was funded by Novartis Healthcare Private Limited and all authors were members of National Steering Committee for the Time2DoMore™ program and received honoraria from Novartis Healthcare Private Limited India for advisory board meetings. Shankar Kumar and Nishan Mathias were employees of Novartis Healtcare Private Limited, India during the time of the initiative.

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CORRECTION

Correction to: RSSDI-ESI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2020

Rajeev Chawla[1] · S. V. Madhu[2] · B. M. Makkar[3] · Sujoy Ghosh[4] · Banshi Saboo[5] · Sanjay Kalra[6] · On behalf of the RSSDI-ESI Consensus Group

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Correction to: Int J Diabetes Dev Ctries (Jan-March 2020) 40 (Supp l):S1-S122
https://doi.org/10.1007/s13410-020-00819-2

In the RSSDI-ESI Consensus Group, Dr Sanjay Bhadada's name was inadvertently missed out as one of the members under the category "Diabetes and CVD".

The corrected list under Diabetes and CVD should therefore read as:

Members: Shaileja Kale, Sudhir Bhandari, R. V. Jayakumar and Sanjay Bhadada.

The online version of the original article can be found at https://doi.org/10.1007/s13410-020-00819-2

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