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Indian Diabetes

EDUCATOR JOURNAL

Theme of the Month

Evolution of Diabetes Treatment Over the Years

To keep Members of Diabetes Care team abreast about
DSME/DSMS - (Diabetes Self management Education/Support) Concepts

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FOREWORD

Research Society for the Study of Diabetes in India (RSSDI) founded by Prof. MMS Ahuja in the year 1972 is the biggest scientific association of healthcare professionals involved in promoting diabetes education and research in India. RSSDI is happy to collaborate with USV to support their endeavour to make India the 'Diabetes care capital of the world'. Through this collaboration, RSSDI would like to strengthen the cadre of diabetes educators by empowering them with recent updates in diabetes management helping bridge the gap between the physician and the patient. Today, the rule of 50% is prevailing in terms of awareness, detection, treatment and control in T2DM. Our aspiration is to achieve 90-90-90-90 i.e.90% of people with diabetes should be made aware, 90% should be detected, 90% of those detected should be treated, and 90% of those treated should reach their goals.

Indian Diabetes Educator Journal (IDEJ) is the first of its kind in India, and the longest running monthly diabetes educator journal since April 2015 and continues its endeavour to spread awareness, knowledge and enable healthcare teams to manage individuals with diabetes and empower them for self-care. RSSDI IDEJ will continue to keep the members of diabetes care team abreast with concepts of Diabetes Self-Management Education/Support (DSME/S) with a reach of 44000 doctors and diabetes educators digitally.

Over the years, the evolution of diabetes treatment has been a testament to medical innovation and dedication. From the discovery of insulin to the development of advanced medications and technologies, the management of diabetes has undergone significant transformation. As we celebrate Doctors' Day on July 1st in India, this issue of IDEJ aims to highlight the invaluable contributions of healthcare professionals in pioneering diabetes care, improving patient outcomes, and fostering hope for a healthier future.

We sincerely thank our contributors for making this issue delightful reading for our readers. We dedicate this journal to all the healthcare professionals who are working relentlessly towards making "India–The Diabetes Care Capital of the World."

Sincere Regards,

Dr. Sanjay Agarwal
RSSDI Secretary

*DSME: Diabetes Self-Management Education, DSMS: Diabetes Self-Management Support

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Article: Insulin Administration Tools: Syringes to Pens to Pumps

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Article: The Evolutionary Journey of Glucose-Lowering Medications for Type 2 Diabetes

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Article: Journey of Diabetes Diagnosis and Classification: From Then to Now

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Article: Frequently Asked Questions on the Evolution of Diabetes Treatment Over the Years

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Issue No. 112, July 2024

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Diabetes Treatment: From Starvation to Modern Therapies

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Diabetes treatment has undergone a remarkable evolution from the era of "starvation diets" to the modern era of advanced therapeutic options. Before the discovery of insulin, physicians advocated the use of herbs, severe fasting, and strict calorie-restricted and low-carbohydrate diets as a desperate measure to manage diabetes. This approach, although controversial and leading to some patients starving to death, was a reflection of the limited treatment options available at that time.

The advent of insulin

The discovery of insulin in the 1920s revolutionized diabetes treatment, marking a significant milestone in the management of the condition. Insulin not only prolonged the lives of patients with diabetes but also transformed diabetes from a fatal diagnosis to a manageable chronic condition. The availability of insulin facilitated a shift from extreme dietary restrictions to more balanced approaches in diabetes management. Over the years, insulin has undergone several modifications to enhance its safety, stability, and duration of action. In the beginning, insulin from cattle and pigs was used, but it caused severe allergic reactions in many patients. The first genetically engineered, synthetic “human” insulin was produced in 1978 using *E. coli* bacteria to produce the insulin. Today, insulin comes in many forms, from regular human insulin to ultra-rapid and ultra-long-acting insulin.

Evolution of oral antidiabetic agents (OADA)

Over the years, diabetes treatment has continued to advance, incorporating technological, biological, and pharmacological innovations. It was in 1955 that the first oral antidiabetic medication, the sulfonylurea (SU) carbutamide, was developed, followed by other drugs in the same class. Then came metformin, and until the early 1990s, only three classes of drugs were available which are insulin, sulphonylureas, and metformin. Several other classes of drugs have been developed since, with the priority not only on glucose-lowering effects but also on cardio and renal protective nature. In today’s age, there are ten classes of OADAs used to treat type 2 diabetes

mellitus (T2DM). These include metformin, SUs, meglitinides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, dopamine agonists, bile acid sequestrants, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, oral glucagon-like peptide-1 (GLP-1) receptor agonists, and dual GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, as well as amylin, which can be administered by injection.

Modern therapeutic landscape

In the contemporary era, diabetes management is multifaceted, encompassing a range of interventions beyond insulin and drug therapy. Lifestyle modifications, including diet and physical activity, play a crucial role in managing diabetes effectively. Non-pharmacological interventions like medical nutrition therapy and bariatric surgery have shown promise in improving outcomes and even bringing about diabetes remission in people with T2DM. Additionally, advancements in diabetes technology, such as continuous glucose monitoring systems and insulin pumps, have enhanced the precision and convenience of diabetes care. The coronavirus disease 2019 (COVID-19) pandemic led to the era of telemedicine, allowing healthcare professionals to manage patients virtually and safely.

Look into the future

Looking ahead, the future of diabetes treatment holds promise with ongoing research into novel therapeutic approaches. A promising option is a β-cell replacement through whole pancreas or islet cell transplantation. Advances in stem cell research have led scientists to differentiate human induced pluripotent stem cells and embryonic stem cells into β-like cells. These cells are capable of secreting insulin-like normal physiological processes. Progress in this field will bring new hope in diabetes management. The use of artificial intelligence is bringing a paradigm shift in diabetes management through data-driven precision care. By leveraging scientific advances and embracing a holistic approach to diabetes management, the goal is to enhance the quality of life for individuals living with diabetes and reduce the burden of this chronic condition on healthcare systems worldwide.

Key points

- The evolution of diabetes treatment from the pre-insulin era to the modern day has been remarkable.
- Insulin's discovery in the 1920s revolutionized management, shifting from extreme dietary restrictions to more balanced approaches.
- Today, diabetes care is multifaceted, including lifestyle modifications, technological advancements like continuous glucose monitoring and insulin pumps, and promising biological and pharmacological innovations.
- Future directions focus on developing interventions that address underlying mechanisms and improve long-term outcomes, aiming to enhance the quality of life for individuals with diabetes and reduce the burden on healthcare systems globally.

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Insulin Evolution in Diabetes Treatment: A Century of Advancements

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The year 2021 marked the 100th anniversary of the momentous discovery of insulin. In January 1922, Leonard Thompson, a 14-year-old boy, received his first injection of animal insulin and survived the complications of diabetes mellitus. Over years of research and advancements, insulin has progressed from crude extracts of the animal pancreas to precise prescriptions of recombinant human insulin and analogs, offering high accuracy and efficacy in administration.

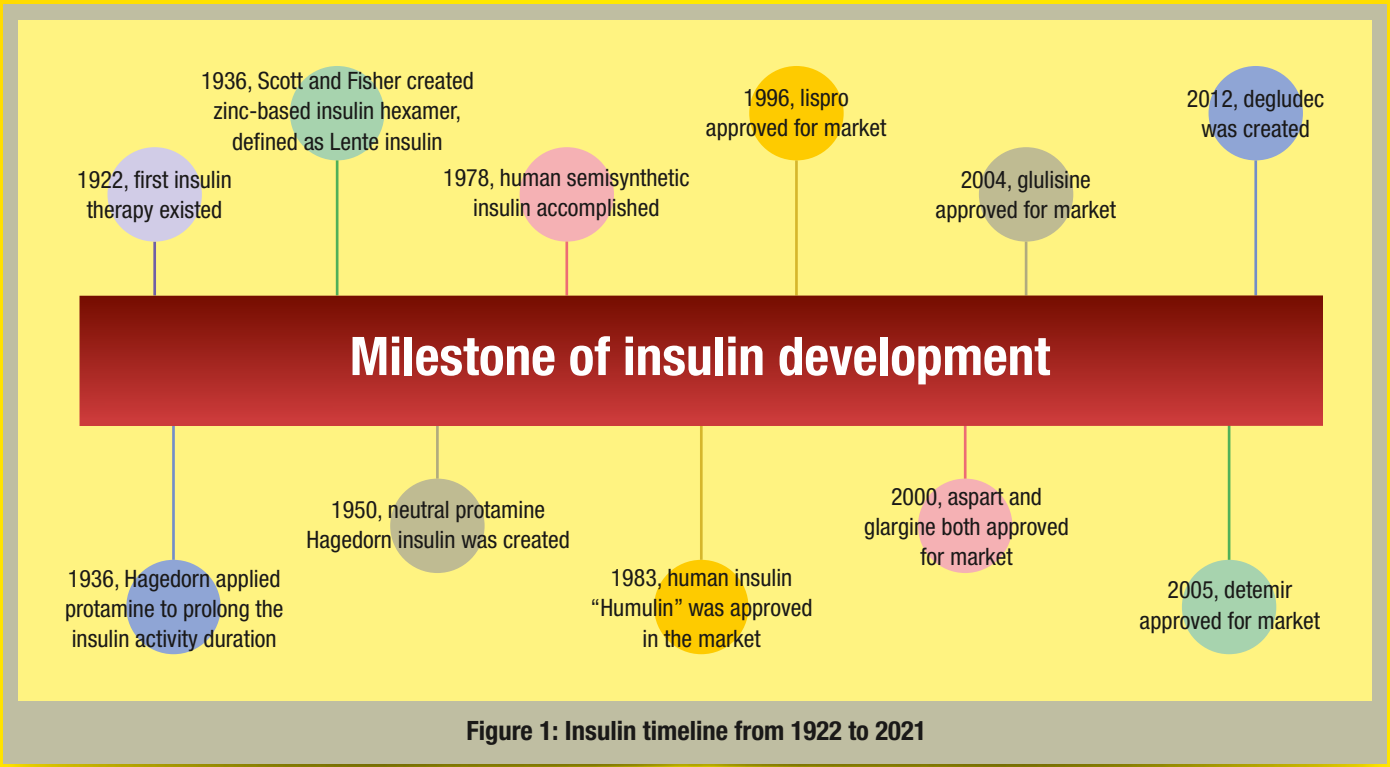

Figure 1: Insulin timeline from 1922 to 2021

Early insulin formulations faced challenges due to impurities causing toxic reactions and limiting clinical use. Efforts to optimize extraction and purification methods led to advancements like the isoelectric precipitation method in 1922, significantly increasing yield and stability. Despite improvements, allergic reactions persisted, prompting further purification steps such as crystallization with metal ions to alleviate allergic reactions. These early insulin preparations, known as regular or soluble insulins, had a short time-action profile, requiring multiple daily administrations. For about 25 years after the first insulin administration in 1922, all formulations remained short-acting until the development of longer-acting basal insulins.

Efforts to extend insulin action initially involved additives like gum solutions and oil suspensions with limited success. Charles Krayenbuhl discovered the "isophane point," leading to neutral protamine Hagedorn (NPH) insulin in 1950, the first widely used

basal insulin. NPH insulin's subcutaneous injection results in a peak action at 5–6 hours with a duration of about 12–13 hours, depending on dosage. However, its proper use requires careful resuspension prior to injection, often underestimated during the NPH era.

The first chemical synthesis of animal insulins took place in the 1960s, followed by the chemical synthesis of human insulin in 1974. In the following years, semi-synthesis of human insulin was achieved. In the 1980s, biosynthetic human insulins emerged, replacing animal insulins. Initial concerns about their safety were raised, but studies showed minimal differences compared to animal insulins. Advances in recombinant deoxyribonucleic acid (DNA) technology led to the development of human insulin analogs with improved safety profiles, offering enhanced efficacy with rare adverse reactions.

Prandial (bolus) insulin analogs

Prandial insulin analogs like insulin lispro, aspart, and glulisine were developed for faster onset and shorter duration of action compared to regular human insulin. More recent faster-acting analogs, like faster aspart and ultra-rapid lispro, result in even earlier and higher peak serum insulin concentrations with shorter durations of action.

Basal insulin analogs

Basal insulin analogs were developed to provide flatter, more stable action profiles compared to NPH insulin. First-generation analogs were insulin glargine 100 U/mL (Gla-100) and insulin detemir that offered prolonged action and were available from 2000 onwards. Later, second-generation analogs such as insulin degludec and insulin glargine 300 U/mL (Gla-300) were developed and aimed for even flatter, more prolonged profiles. Degludec delays absorption via hexamer formation, while Gla-300, being three times more concentrated than Gla-100, forms a smaller subcutaneous depot, resulting in slower absorption and more prolonged action. These analogs offer enhanced stability and duration, contributing to improved glycemic control in diabetes management.

Summarizing insulin advancements over the last century, early insulin formulations encountered purification challenges that restricted yield and production capacity. This resulted in unpredictable time-action profiles and difficulties in glucose monitoring. However, innovations like recombinant DNA technology facilitated the synthesis of human insulin and analogs, revolutionizing diabetes management by enhancing efficacy and safety.

Key points

- Insulin was first discovered in 1921.
- Early insulin formulations contained impurities, but advancements, such as the isoelectric precipitation method in 1922, improved yield and stability.
- Biosynthetic human insulins replaced animal insulins in the 1980s, driven by therapy intensification and advances in recombinant DNA technology.

- Basal insulins, starting with NPH insulin in 1950, offered longer action but required careful resuspension prior to injection.
- Prandial insulin analogs like lispro, aspart, and glulisine offer faster onset and shorter duration compared to regular insulin.
- Basal insulin analogs were developed to provide flatter, more stable action profiles compared to NPH insulin. The first-generation basal insulin analogs were glargine and detemir. Second-generation basal insulin analogs, including degludec and glargine 300 U/mL, offer even flatter, prolonged profiles, improving glycemic control.

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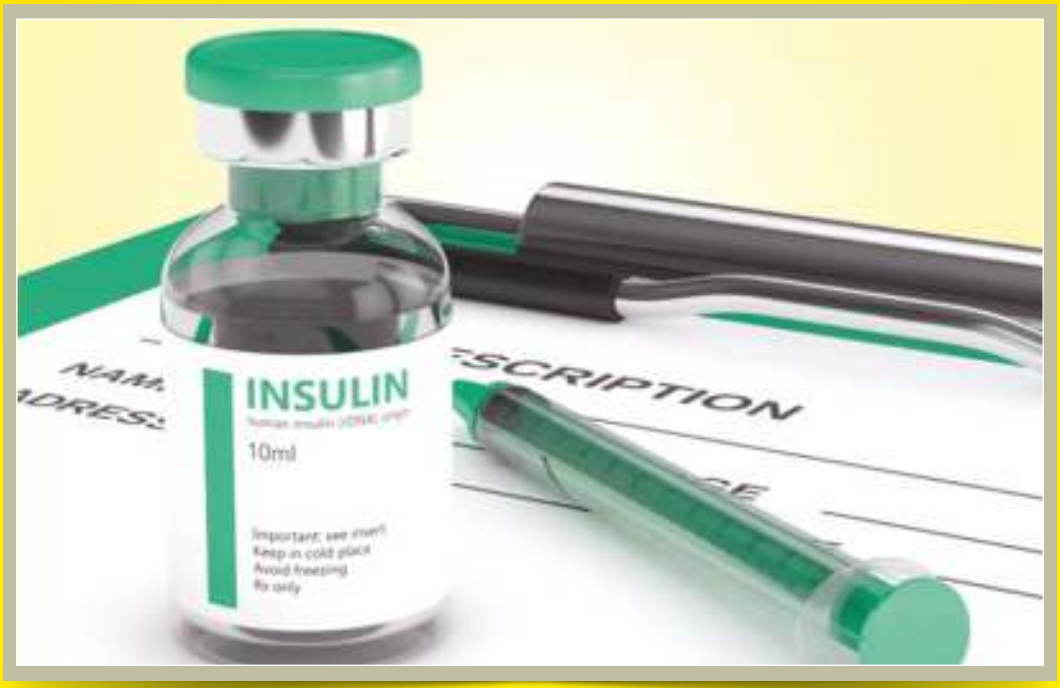

Medical Nutrition Therapy in Diabetes: Then and Now

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Diet has been crucial in treating diabetes since ancient times, as seen in the Ebers Papyrus from 1500 BC, which recommended wheat grains, berries, grapes, and honey. Over the years, dietary interventions evolved with insulin therapy, blood glucose monitoring, dietary trends, and quality of life considerations.

Dietary approaches before the discovery of insulin	In ancient times, diets favored plants over meat, with Willis promoting energy restriction, leading to the starvation diet concept. Carbohydrates weren't understood, but fruits, veggies, and cereals were emphasized. In the 19th century, John Rollo introduced the first low-carb diet, focusing on milk, meat, and fat. Various food cures emerged but failed due to poor adherence. In the 20th century, low-carb diets for people with diabetes were introduced but faced challenges. These diets were unpopular and often abandoned quickly.
Dietary practices during the 1920s: The period marked by carbohydrate limitation	Insulin's discovery revolutionized diabetes treatment, initially focusing on survival and then on maintaining normal blood glucose levels. Low-carb, high-fat diets persisted post-insulin introduction to minimize glycosuria and reduce insulin costs. People with diabetes weighed food meticulously, supported by educational handbooks. Various dietary strategies emerged, but adherence remained a challenge. Early insulin therapy using impure animal insulin led to blood glucose control issues and introduced hypoglycemia risks.
Dietary patterns in the 1930s: Carbohydrate restriction and unrestricted diets	Soluble insulin purification in the late 1920s led to multiple daily injections (MDIs) and the development of longer-acting insulins like protamine zinc insulin (PZI) in the 1930s. Some could manage with one daily injection, but many still needed soluble insulin at meal times. Surprisingly, higher carbohydrate intakes were found to reduce insulin requirements, leading to the concept of free diets. These allowed more food flexibility, including higher carb intake, with sufficient insulin for control. Traditionalists prioritized blood glucose control, while free diet advocates emphasized quality of life and reduced hypoglycemia risk.
Dietary practices between 1940 and 1960: Carbohydrate guidelines and the avoidance of sugar	In the following decades, carbohydrate restriction became common for people with diabetes. In a 1953 UK survey, 25% of clinics suggested diets with only 20% of energy from carbs, while most advised 30%–40%. Guidance focused on "free foods" like meat, fish, eggs, cheese, veggies, fats, and low-carb fruits, while sugars were avoided. Starchy carbs and natural sugars were limited using exchange lists. In the UK, one carb exchange equaled 10 g, while in the US, it was 15 g. Dietitians were involved, but the physician-led model persisted, with diets often prescribed.
Dietary trends in the 1970s and 1980s: High fiber and introduction of the concept of glycemic index (GI)	Insulin therapy initially promised good health for people with diabetes, but complications from suboptimal glycemic control emerged. Debate ensued on the role of diets, focusing on high-fat and low-fiber intake contributing to cardiovascular disease risk. In the 1970s–80s, guidelines from organizations like the American Diabetes Association (ADA) advocated higher carb and fiber intake, lower fat and salt intake, and excluding free sugars except for treating hypoglycemia. The 1980s introduced the concept of GI, emphasizing the varied effects of carbs on postprandial glucose. Low GI diets gained popularity, though debated. Self-monitoring of blood glucose (SMBG) and glycated hemoglobin (HbA1c), which were introduced in the early 1980s, improved dietary assessment. New human insulins provided flexibility in diabetes management.

Dietary practices in the 1990s: The Diabetes Control and Complications Trial (DCCT)	The landmark DCCT of 1993 conclusively addressed the importance of glycemic control in preventing diabetes complications. The intensively treated group, maintaining HbA1c levels of 7.2%, experienced significant reductions in retinopathy, neuropathy, and nephropathy. However, this was offset by a threefold increase in hypoglycemic events and an average weight gain of 4.6 kg. The intensive therapy group employed MDIs and regular SMBG and received detailed dietary advice and support. DCCT applied a combination of four dietary interventions. Adoption of diet-related behaviors correlated with improved glycemic control, highlighting the effectiveness of the interventions despite adherence challenges.
Dietary trends in the 2000s: Dietary flexibility and the practice of carbohydrate counting	Before the DCCT, a group in Germany utilized an intensive education program promoting carbohydrate counting and insulin adjustment for 10 years, resulting in improved glycemic control and reduced hospital admissions. This approach influenced the Dose Adjustment for Normal Eating (DAFNE) study in the UK, advocating for unrestricted dietary choices for people with diabetes. The DAFNE study demonstrated improved glycemic control, dietary freedom, quality of life, and treatment satisfaction without increasing hypoglycemia, weight, or lipid levels.
Current dietary practices: Personalized for each individual	Carbohydrate management, rather than restriction, is now the recommended approach for all people with diabetes. The "one size fits all" approach is no longer valid, and diets for each individual are customized. Following the success of the DAFNE study, carbohydrate counting and insulin adjustment have become widely recommended strategies, although long-term management issues persist. There's renewed interest in low and very low-carbohydrate diets for diabetes management, with some clinical audits suggesting positive effects on glycemic control. However, these diets cannot be universally recommended and need the supervision and guidance of healthcare professionals.

Medical nutrition therapy has always been and continues to be a pillar in diabetes management. While there is nothing like a "diabetic diet," the focus today is on healthy eating and individualized advice based on many related factors, keeping compliance, convenience, and outcomes in mind.

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- Dyson P. Type 1 diabetes: Dietary modification over 100 years since insulin. *Practical Diabetes*. 2021;38(4):40-44. doi:10.1002/pdi.2351

Future of Diabetes Care

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The field of artificial intelligence (AI) is rapidly expanding, offering promising solutions for addressing the global epidemic of diabetes. By leveraging machine learning principles, algorithms are being developed to create predictive models for diabetes risk assessment and management of its complications. Digital therapeutics are emerging as effective lifestyle interventions, empowering patients to better manage their condition independently. AI-enabled tools enable continuous remote monitoring of patients' biomarkers and symptoms, while social media and online forums enhance patient engagement in treatment.

Technological advancements are optimizing resource utilization in diabetes management, leading to more efficient care delivery. These innovations collectively contribute to improved glycemic control by reducing glucose excursions, glycosylated hemoglobin levels, and fasting and postprandial glucose levels. With AI, the landscape of diabetes treatment is poised for a transformative shift toward data-driven precision care, departing from traditional management approaches.

A recent panel discussion at the American Diabetes Association (ADA) 2023 titled **"The Future of Diabetes Care"** explored various potential developments, including the following.

- Immunological therapies to delay or prevent type 1 diabetes
- Wearable technology
- Advancements in drug therapies for glucose regulation and complication reduction
- Cell replacement therapies

Also, future innovations can greatly improve insulin therapy. Weekly insulins are coming soon, and liver-targeted and oral options are promising but face challenges. Smart insulins that respond to glucose levels will take longer to develop.

Despite significant progress since the first administration of insulin over a century ago, the journey toward enhancing the lives of individuals with diabetes and ultimately finding a cure continues.

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Interview with Dr. C. H. Vasanth Kumar

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Dr. C. H. Vasanth Kumar is a highly esteemed physician based in Hyderabad with over 40 years of exemplary medical practice. His leadership roles, including past chairman and executive committee member of the Hyderabad chapter of the Association of Physicians of India and past president of the Research Society for the Study of Diabetes in India (RSSDI), underscore his commitment to advancing healthcare. As the founder and president of the Diabetes And You (DAY) Society, he extends support to underprivileged individuals, particularly children with type 1 diabetes. Dr. Kumar actively engages in public health initiatives, delivering lectures and organizing health camps at government schools. With a passion for improving healthcare standards and medical education in India, he serves as a senior consultant physician at Apollo Hospitals, Hyderabad. His journey is defined by the relentless pursuit of excellence in healthcare, coupled with a steadfast resolve to make a meaningful difference in the lives of individuals and communities he serves.

Evolution of Diabetes Treatment Over the Years

1. Since how many years have you been treating people with diabetes, and what inspired you to specialize in this field?

Ans. I have been a practicing physician for the last four decades. It is the gradual increase in the incidence of diabetes, which goes undetected in many or uncontrolled in many, which necessitated me to take up this task.

2. In your experience, what have been some of the most significant breakthroughs or advancements in diabetes treatment over the years?

Ans. In the last 40 years, there have been many developments in the management of diabetes. One of the remarkable ones was self-glucose monitoring after the advent of glucose monitoring devices. It changed the lives of people with type 1 and type 2 diabetes who are on insulin. Newer medications like dipeptidyl peptidase-4 (DPP-4) inhibitors and

sodium-glucose cotransporter-2 (SGLT-2) inhibitors have remarkably reduced the need to give insulin to many people with uncontrolled diabetes. We have also seen better insulins that are available, especially the discovery of basal analogs and the new delivery systems of insulins like pens and pumps.

3. How have you adapted your own clinical practice in response to the advancements in diabetes treatments through the years?

Ans. One just needs to remain updated and see how we can help our patients. This always involves using wisdom to differentiate every patient, who is different from the others in many ways, such as age, weight, attitude, and socioeconomic status.

4. What are some of the ongoing challenges or areas of unmet need in diabetes treatment, and what efforts are being made to address them?

Ans. There are many challenges and unmet needs, like a lack of awareness about the disease, lack of proper facilities, and poor training facilities for health care professionals at the primary care level, resulting in improper management of the disease in rural areas and urban slums where diabetes is prevalent. Many breakthroughs are already happening. What is challenging is to selectively apply them to those who require them.

5. How do you envision the future of diabetes treatment evolving, and what potential breakthroughs or innovations do you anticipate?

Ans. We will see many developments in technology and the application of artificial intelligence (AI), which will result in better monitoring and management of diabetes. We will also see more effective and safer drugs to prevent and manage diabetes in the future.

Insulin Administration Tools: Syringes to Pens to Pumps

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The year 2021 marked the 100th anniversary year of insulin's discovery. Still, the most effective and safest glucose-lowering treatment remains insulin. Despite its effectiveness, the main problem with insulin has been hypoglycemia, which has led to the prescription of suboptimal dosages in many patients. Syringes, pens, and pumps are common insulin administration tools. It is anticipated that in the near future, an artificial pancreas (AP) with a closed-loop delivery system and >95% time in range will be possible. Recent developments in computer algorithms and continuous glucose monitoring (CGM) have accelerated the development of closed-loop delivery systems.

Insulin delivery devices: Syringes

The Hypak™ (Becton, Dickinson and Co., Franklin Lakes, NJ) was the first disposable glass syringe and was first introduced in 1954 for use in polio vaccination. It was later found to be used in the administration of insulin. In 1955, Rohr Products Inc., Waterbury, CT, introduced the all-plastic Monoject™ syringe. By the mid-1960s, a number of manufacturers were selling disposable plastic syringes, which were widely used. The development of hypodermic needles, blood glucose meters, and medications have all made it possible to treat diabetes better; nonetheless, "traditional" syringe technology has not altered much since the latter quarter of the 20th century.

Insulin pens

Pens provide greater flexibility, precision, discretion, and long-term cost-effectiveness than syringes, which enhances treatment adherence and persistence. As a result, the use of insulin pens has gained acceptance and shows improved glycemic control.

The inconvenience and error in preparing the insulin doses limit the usage of vial and syringe insulin injections. Insulin pens were developed as a result of these problems. Novo Nordisk produced the first insulin pen in 1985.

The more recent insulin pens are more accurate and reusable. They also have safety features like loud clicks with every dose to increase precision and

lower the possibility of human error. We now have pens with half-unit dosage and an easy-to-use design to boost confidence in kids and parents. Because of this, insulin pens are more expensive than vials and syringes but also more precise, practical, painless, and patient-friendly.

Continuous subcutaneous insulin infusion (CSII)

Kadish created the first portable insulin pump in 1963, but its functionality was restricted by its size and technological problems. In the USA, the first commercial insulin pump was unveiled in 1979.

The functional aspect of CSII is the administration of insulin through an infusion system connected by tubing to a subcutaneously implanted cannula, typically into the stomach. The insulin pump is composed of four main components: A small computer that is programmed to dispense insulin; a disposable plastic reservoir that can hold up to 300 units of insulin; a screw-drive mechanism that moves the insulin through the tubing at variable rates; and a battery that provides power. Bolus injections are given before meals and snacks, while a continuous slow infusion of fast-acting insulin analogs is utilized to replicate basal secretion using the insulin pump system. This can be customized for every patient. The newer generation of insulin pumps has smaller dimensions and intelligent features like alarms and dose calculators integrated right into the device, making them more patient-friendly.

Sensor-augmented pump (SAP) therapy

Combining the use of a pump and continuous glucose monitor (CGM) for diabetes control is now possible due to advancements in CGM technology. The most recent iterations of CGMs have been demonstrated to enhance glycemic control in type 1 diabetes patients. SAP therapy involves using CGM signals to modify insulin administration via an insulin pump.

SAP (with low glucose suspend or threshold suspend [TS] pump)

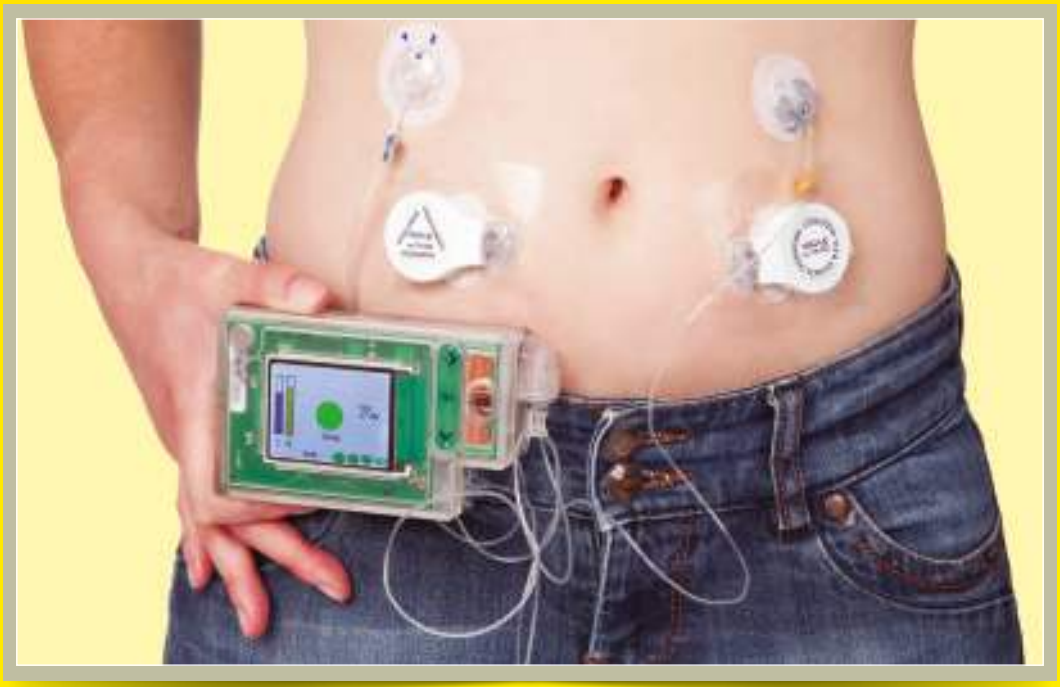
CSII, SAP, and multiple daily injections (MDI) cannot completely eradicate nocturnal hypoglycemia. To prevent night-time hypoglycemia, the first step is creating an AP (closed-loop system) that stops delivering insulin once CGM glucose reaches a low threshold (often 70 or 60 mg/dL). If a patient ignores a low glucose alert, the TS system stops delivering insulin for up to two hours. This function will not only prevent hypoglycemia; rather, it is intended to lessen its severity and duration.

Artificial pancreas (AP)

The main goal of CSII has been to create an AP that can replicate superior glucose regulation with the least amount of human intervention. A "closed-loop," often known as an AP, is a system of advanced technologies that activate automation to meet glycemic targets. AP often connects three devices.

- A sensor, such as a CGM, that detects blood glucose and transmits data to a computer algorithm.
- A control algorithm that evaluates the data and determines the necessary insulin dosage.
- An insulin infusion pump that administers insulin in accordance with computer commands.

The goal of technology advancements is to achieve 100% time in range (TIR) and 0% time in hypoglycemia, starting with syringes and pens and moving up to pumps and AP.



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Personalized Counseling for Building Confidence in the Right Injection Technique: A Doctor's Experience on the MyCare Patient Support Program

Dr. Shardul Kothary

MBBS, D. Diabetology (Gold Medalist)
Consulting Diabetologist, Sushrusha Hospital, Dadar (W) and Mata Laxmi Hospital, Sion (E)

A gentleman with type 2 diabetes is managed by Dr. Shardul Kothary.

Here's what Dr. Shardul has to say:

I was approached by a patient with uncontrolled blood glucose readings who was also suffering from herpes in the eye. I put him on insulin therapy for better control of blood glucose levels. He and his wife were very apprehensive about starting insulin injections. I advised them to enroll in the MyCare program, through which I have received continued support and have seen good outcomes for my patients. They met a MyCare Diabetes Educator (MDE), Ms. Purvi Gala.

The MDE took a detailed history to understand the case. She realized that this patient was a foodie, so she made sure to plan a customized diet based on his liking, keeping in mind a low glycemic index diet with adequate protein. The diet was planned to aim at better blood glucose control as well as faster recovery from infection while still keeping the patient satisfied. When the patient first met the MDE, his fasting blood sugar (FBS) reading was 165 mg/dL, postprandial (PP) was 200 mg/dL, and random sugar was 195 mg/dL. After my intervention and counseling by the MDE, his current values are FBS 115 mg/dL, and random sugar is 116 mg/dL. He is also recovering well from the infection. The MDE made special efforts to explain all the aspects of insulin injecting techniques, storage of insulin, and care to be taken to avoid lipohypertrophy. She gave them the confidence to take insulin without any fear, ensuring that it was the best and safest treatment option for him.

Ms. Purvi Gala

NDEP and T1DE Certified Diabetes Educator

Here's what the MDE Purvi Gala has to say:

Understanding the patient and then modifying the diet based on one's lifestyle and personal liking helps in compliance and gives better outcomes. Also, handholding and counseling the patient until they are confident enough to take insulin without fear helped in bringing about faster recovery from infection with better glucose control.

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*PwD: People with Diabetes

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CVD- Cardiovascular Disease HF- Heart Failure CKD- Chronic Kidney Disease
*L Ravikumar et al., Cardiol Cardiovasc Med 2023; 7: 141-144. no no. of patients | #As per the literature search (PubMed and Google Scholar) on 27th March 2024

Reference: 1. Singh AK, et al., Endocr Pract. 2023 Jul;29(7):509-516.

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Advances in Blood Glucose Monitoring Over the Years

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Diabetes is a chronic condition affecting millions worldwide. Effective management of diabetes relies heavily on monitoring blood glucose levels regularly. Over the years, significant strides have been made in blood glucose monitoring technology, enhancing the accuracy, convenience, and comprehensiveness of monitoring tools.

History of glucose monitoring

Efforts to quantify glucose started in the mid-1800s. Glucose in the urine was determined by evaporating urine to find sugar crystals. In 1908, Benedict developed a copper reagent for assessing glucose in the urine, and eventually, tests for glycosuria were commercialized.

In 1965, the Ames research team headed by Anton Clemens developed Dextrostix, the first blood glucose test strip. The first glucose meter was used in the 1970s with the Dextrostix, but its accuracy was poor. By the mid-1970s, the concept of patients doing blood glucose monitoring at home was contemplated. By 1980, the Dextrometer was launched; this meter used the Dextrostix along with a digital display. Eventually, self-monitoring of blood glucose (SMBG) became the standard of care for diabetes. SMBG technology continued to improve through the late 1980s, 1990s, and early 2000s. By 2010, SMBG had become virtually painless and convenient to use, with good precision.

Continuous glucose monitoring (CGM)

While effective, SMBG has limitations, such as providing only point-in-time measurements and requiring frequent calibrations. In contrast, CGM systems provide real-time glucose data, offering users insights into current glucose levels and rate of change trend arrows. This real-time feedback enables prompt responses to glycemic fluctuations, mitigating acute glycemic events effectively.

Types of CGM systems

CGM systems can be categorized into two types, namely, real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), also known as "flash" CGM. rtCGM systems, such as the Dexcom G6, Medtronic Guardian Sensor 3, and Senseonics Eversense, offer CGM with real-time alerts for high and low glucose levels. isCGM systems, like the FreeStyle Libre, require users to scan the sensor to obtain glucose data but do not provide real-time alerts. Both types have revolutionized diabetes management by providing users with greater control and insight into their glucose levels.

Advancements in CGM technology

Advancements in CGM technology have led to improved accuracy, smaller and less invasive devices, extended sensor life, and approval for insulin dose decisions. These improvements have increased patient satisfaction, adherence, and integration with insulin delivery systems. Moreover, new CGM-based glycemic metrics provide comprehensive information beyond SMBG and glycated hemoglobin (HbA1c), enabling personalized diabetes management strategies.

Future directions

Research is underway on non-invasive glucose monitoring methods, utilizing sweat and tear fluid as testing mediums. These developments hold promise for the creation of implants and wearables for continuous monitoring, enhancing the wearability, precision, and accessibility of CGM systems. Additionally, ongoing advancements in biosensor technology continue to push the boundaries of blood glucose monitoring, paving the way for further improvements in diabetes care.

Advances in blood glucose monitoring technology have revolutionized diabetes care, providing individuals with diabetes with more accurate, convenient, and comprehensive tools to manage their condition effectively. From testing urine to traditional SMBG methods to cutting-edge CGM systems, the evolution of blood glucose monitoring has transformed the landscape of diabetes management. With continuous innovation and research, the future of blood glucose monitoring holds promise for improving the quality of life for individuals with diabetes.

Key points

- Diabetes management has evolved from testing urine to traditional finger-stick measurements to test blood glucose to CGM, providing real-time glucose data.
- CGM systems come in two types, namely, rtCGM and isCGM, both offering continuous monitoring capabilities.
- Advancements in CGM technology include improved accuracy, smaller devices, longer sensor life, and integration with insulin delivery systems.
- Future directions include research on non-invasive methods and biosensor technology, promising implants, and wearables for continuous monitoring.
- Overall, CGM technology revolutionizes diabetes care, providing accurate, convenient, and comprehensive information for effective management.

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The Evolutionary Journey of Glucose-Lowering Medications for Type 2 Diabetes

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Type 2 diabetes mellitus (T2DM) has plagued humankind for centuries. The discovery of insulin in 1921 caused a paradigm change in diabetes management, moving away from rigorous starvation diets to successful blood glucose control. It also gave recognition to insulin resistance and led to the categorization of T2DM.

The year 1955 marked a turning point with the introduction of the first oral antidiabetic drug (OAD), sulfonylurea (SU) carbutamide, which later expanded to chlorpropamide, tolbutamide, glipizide, glyburide, and glimiperide. Metformin, the first insulin sensitizer, debuted in Europe in 1957 and reached America in 1995. Interestingly, for nearly four decades until the early 1990s, only metformin and SUs, along with insulin, were available for the management of diabetes.

In the mid-1990s, alpha-glucosidase inhibitors (acarbose, miglitol, and voglibose) and meglitinides (nateglinide and repaglinide) were introduced as some of the first OADs, sharing similarities with SUs but with shorter half-lives. Following in the late 1990s and early 2000s were the peroxisome proliferator-activated receptor γ (PPARγ) agonists and thiazolidinediones (TZDs). However, troglitazone was removed from the market due to liver damage concerns. Subsequent apprehensions about rosiglitazone's cardiovascular (CV) safety led to its withdrawal, and the Food and Drug Administration's (FDA's) mandate for all diabetes medications to demonstrate CV safety. Pioglitazone, known for its benefits in preventing diabetes and stroke, remains available but is limited in its widespread use due to risks of edema, fractures, and precipitating heart failure (HF).

Human insulin analogs emerged at the cusp of the 21st century, followed swiftly by a range of short- and long-acting analogs. In 2005, the injectable amylin analog pramlintide debuted alongside oral incretin class drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, vildagliptin, saxagliptin, linagliptin, sitagliptin) in 2006. Additional medications introduced in the late 2000s include colesevelam, a bile acid sequestrant activating liver farnesoid receptors, in 2008 and bromocriptine, which stimulates hypothalamic dopamine receptors, in 2009.

The most notable drug categories introduced during the 2000s include glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and dual GLP-1 receptor and gastric inhibitory polypeptide (GIP) receptor agonists (GIP/GLP-1RAs). In 2022, tirzepatide, the inaugural medication combining GIP and GLP-1RA, obtained FDA approval for treating adults with type 2 diabetes (T2DM). Tirzepatide not only leads to substantial weight loss comparable to that seen post-bariatric surgery but also prompts diabetes remission.

Agitation regarding the CV safety of OADs escalated when a meta-analysis exposed a potential association between the widely prescribed rosiglitazone and increased risks of myocardial infarction and CV death. Adhering to FDA directives, multiple extensive cardiovascular outcomes trials (CVOTs) were conducted. Findings from these trials not only demonstrated the effective reduction of blood glucose levels but also showed that SGLT-2 inhibitors and GLP-1RAs notably enhance clinically significant CV and renal outcomes. The CVOT investigating semaglutide is presently underway, with anticipated results slated for 2024.

Both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend SGLT-2 inhibitors and GLP-1RAs as first-line treatments to reduce the risk of cardiorenal complications in high-risk individuals with or without metformin use. The European Society of Cardiology (ESC) guidelines also suggest SGLT-2 inhibitors or GLP-1RAs as initial therapy for those with T2DM at high CV risk instead of metformin. However, it's worth noting that the majority of participants in CVOTs were already taking at least one glucose-lowering medication, primarily metformin, at the beginning of the studies.

Presently, the array of available OADs, each targeting distinct pathological pathways, underscores the efficacy of combination therapy over monotherapy, owing to synergistic effects. According to the Research Society for the Study of Diabetes in India (RSSDI) 2022 guidelines, a patient-centered approach favors dual therapy options like SGLT-2 inhibitor, DPP-4 inhibitor or, SU or TZDs, alpha-glucosidase inhibitors (AGI) or oral GLP-1RA for second-line treatment. If targets aren't met, triple or quadruple therapy can be started, involving a third oral agent such as AGI, DPP-4 inhibitor, SGLT-2 inhibitor, TZDs, or oral GLP-1RA.

The journey of glucose-lowering medications for T2DM has seen remarkable evolution. The recent introduction of GLP-1RAs and SGLT-2 inhibitors, with drugs like tirzepatide showing promise in weight loss and diabetes remission, have minimized the popularity of SUs due to side effects like weight gain and hypoglycemia. Unfortunately, they remain inaccessible to the majority of the patients due to their high cost. The availability of generic versions, along with enhanced education, may increase their usage.

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Journey of Diabetes Diagnosis and Classification: From Then to Now

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For centuries, mankind has been familiar with diabetes. Over a period of time, a number of prominent scientists have tried to explain the symptoms, pathogenesis, diagnosis, and different treatment strategies. Over a period of time, the diagnosis of diabetes and its classification has undergone advancements.

The journey in the progression of diabetes diagnosis

Ayurvedic scientists Sushruta and Charaka, in the early 5th and 6th century, first observed and defined diabetes by its characteristic feature of sweet-tasting urine, described as "Madhumeha" or "honey urine." Further, in the 1600s and 1700s, Paracelsus and two European scientists, Thomas Willis and William Cullen, respectively, made an effort to define diabetes. Additionally, Joseph von Mering and Oskar Minkowski's research with dogs was able to confirm the diabetes diagnosis when urine was analyzed for sugar. This finding announced the pancreas's involvement in diabetes. Investigators in the 1800s, Apollinaire Bouchardat and E. Lancereux, made significant progress in understanding and classifying diabetes, thus predicting a far better prognosis. In 1955, Philip Hugh-Jones elucidated R. D. Lawrence's (1950) classification and coined the terms "type 1" and "type 2" diabetes. In 1979, the US Diabetes Data Group, also known as the National Diabetes Data Group (NDDG), reviewed epidemiological studies and found a link between blood glucose levels and diabetes-related complications like retinopathy and nephropathy. Based on this correlation, the NDDG set diagnostic blood glucose targets. The American Diabetes Association (ADA) defined new diagnostic criteria for diabetes in nonpregnant individuals is as mentioned below.

Table 1: Diagnostic criteria for diabetes in nonpregnant individuals

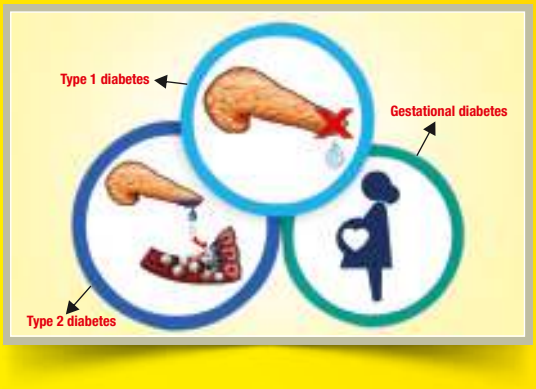
A1C ≥6.5% (≥48 mmol/mol) or
FPG ≥126 mg/dL (≥7.0 mmol/L) or
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT or
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose ≥200 mg/dL (≥11.1 mmol/L)

Abbreviations: A1C: Glycated hemoglobin; FPG: Fasting plasma glucose; 2-h PG: 2-hour plasma glucose; OGTT: Oral glucose tolerance test

The journey in the development of diabetes classification

Over the past century, there have been significant advancements in the understanding of diabetes. With no formal classification of diabetes before the 1960s, the first World Health Organization (WHO) study on diabetes classification was released in 1965 by the expert committee on diabetes mellitus, which marked one of the initial efforts toward an international consensus on the classification of diabetes. A revised classification of glucose intolerance was developed by the NDDG and later modified and adopted by the WHO expert committee in 1980, introducing insulin-dependent diabetes mellitus (IDDM) as type 1 and non-insulin-dependent diabetes mellitus (NIDDM) as type 2 as the two main types of diabetes mellitus.

The 1985 WHO study group report omitted "type 1" and "type 2," retaining "IDDM" and "NIDDM" and introducing “MRDM" (malnutrition-related diabetes mellitus). This classification relied heavily on clinical descriptions, emphasizing pharmacologic treatments for various patient types, including gestational, non-insulin-dependent, and insulin-dependent, and included gestational diabetes mellitus (GDM), other diabetes forms, and impaired glucose tolerance (IGT). In 1999, the WHO adopted Kuzuya and Matsuda's approach, distinguishing criteria based on insulin absence/action and etiology. Over time, "IDDM" and "NIDDM" were phased out as they caused confusion for healthcare professionals, thus focusing more on age and therapy rather than pathogenesis.



In the currently accepted classification, "type 1" and "type 2" continue to be used. Based on its etiology, diabetes falls into the following main categories according to the most recent ADA 2024 classification: Type 1 diabetes (caused by autoimmune β-cell destruction that typically results in absolute insulin deficiency, including latent autoimmune diabetes of adulthood), type 2 diabetes, and other specific types of diabetes arise from various causes, such as monogenic diabetes syndromes (like neonatal diabetes and maturity-onset diabetes of the young), disorders affecting the pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as, due to glucocorticoid use, human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS] treatment, or post-organ transplantation) and gestational diabetes mellitus, which is defined as diabetes mellitus detected in the second or third trimester of pregnancy but not clearly evident before gestation.

The development in the identification, diagnosis, and classification of diabetes has evolved, and this has had a significant impact on reforming the management of diabetes. Early diagnosis and a targeted treatment strategy based on the type of diabetes help prevent complications and improve the quality of life of people living with diabetes.

Key points

- Diabetes, known for centuries, was identified in ancient times by sweet-tasting urine or symptoms such as excessive urination and thirst.
- Over time, numerous scientists described symptoms, pathophysiology, and treatments with varying success.
- Current classification emphasizes etiology and pathogenesis for effective treatment globally.
- Evolving diagnostic criteria reflect a deeper understanding of disease mechanisms.
- Recent research promotes personalized diabetes management and early identification of high-risk individuals.

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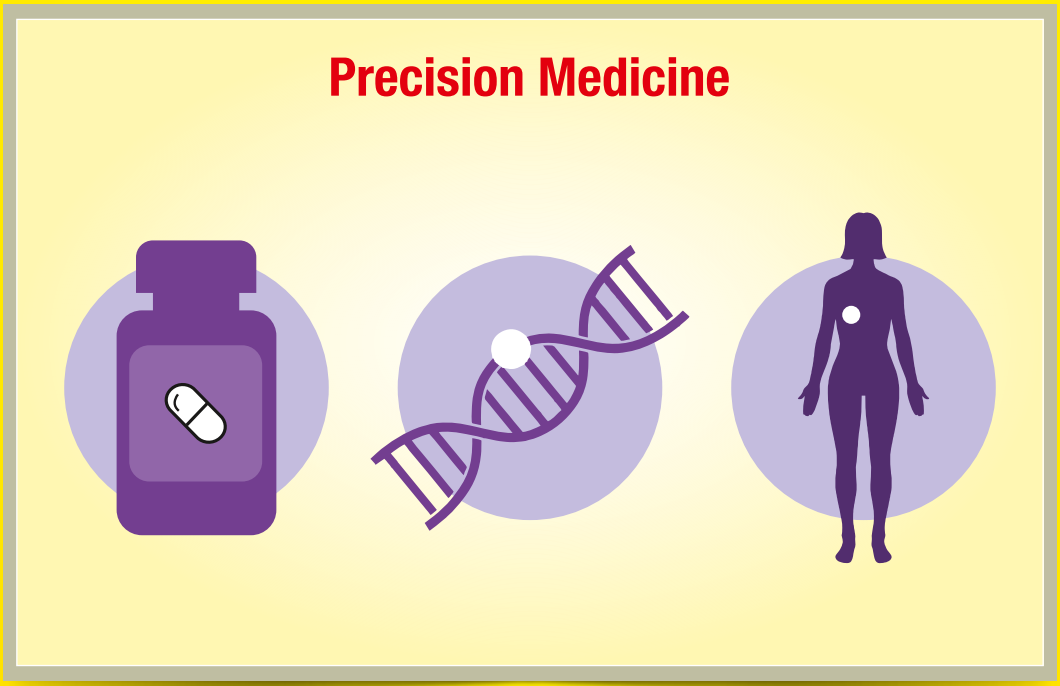

Frequently Asked Questions on the Evolution of Diabetes Treatment Over the Years

Dr. K. M. Jeedhanderan

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1. I am a 52-year-old man having diabetes for the last 8 years. Recently, my blood glucose levels have been uncontrolled, and the doctor has suggested insulin for me. My concern is that I am very conscious about my weight and try to maintain it. I have heard insulin causes weight gain. Is this true?

Ans. When blood glucose levels remain high for a prolonged time, weight loss may occur because glucose cannot effectively provide the necessary energy when it's unable to enter body cells due to insufficient insulin. Insulin therapy facilitates the efficient utilization of blood glucose, allowing it to enter cells and fulfill its role in providing energy. As a result, some individuals starting insulin treatment may experience slight weight gain as their blood glucose levels come down. However, if the insulin dosage aligns with food intake, excessive weight gain typically does not occur unless an individual is taking more insulin than necessary. Following a well-balanced, calorie-controlled diet recommended by a qualified dietitian alongside insulin therapy generally does not lead to excessive weight gain.

2. I am a 45-year-old individual diagnosed with type 2 diabetes mellitus. My doctor has advised me to start a new medication during breakfast and dinner called alpha-glucosidase inhibitor. What does this drug do, and what precautions do I need to take while adding this drug to my routine?

Ans. Alpha-glucosidase inhibitors (AGIs) slow down carbohydrate breakdown and absorption by inhibiting the enzyme alpha-glucosidase required to digest the carbohydrates. As a result, the carbohydrates may get partially broken down and can get fermented to cause gastrointestinal side effects like flatulence, diarrhea, abdominal pain, and bloating.

These symptoms worsen with sugar-sweetened beverages and high-carbohydrate diets due to increased fermentation. It's best to avoid foods known to cause excess gas, like cruciferous vegetables. AGIs are recommended for managing postmeal hyperglycemia. Hence, moderate carbohydrate intake is advised, and one must not go on low-carbohydrate diets or keto diets when this medication is being taken to avoid hypoglycemia. Another point to remember is that if you do experience hypoglycemia, it must be corrected with simple carbohydrates such as glucose. It is advisable not to correct with sugar as the medicine does not let the enzyme that breaks down sugar work, and so it will take time for absorption, which is not recommended in hypoglycemia.

3. I am a 16-year-old individual with type 1 diabetes. My college is going on an industrial visit, and I wanted to know what is the right way to store insulin while traveling and what I need to be mindful of while carrying my insulin along with me.

Ans. Proper storage and transportation of insulin are crucial to maintaining its effectiveness. Here are some key guidelines.

- When traveling, use an insulated bag or cooling pouch. Insulin is sensitive to extreme temperatures. Heat can damage insulin, insulin pumps, and other diabetes equipment. Do not leave them in extreme heat, especially during summer, or in cars for extended periods.
- Unused insulin pens and vials should be refrigerated (2–8°C) until opened. After opening, insulin can be stored at room temperature up to 30°C or in insulin cooling pouches. If a refrigerator is not available while traveling, unopened insulin can be wrapped in a plastic bag and stored in a small bowl of water.
- Before each use, inspect insulin for changes in color, clarity, or the presence of crystals. Clear insulin should always remain clear and never become cloudy.
- Carry insulin in hand luggage when traveling by air to avoid exposure to extreme temperatures in the cargo compartment. Avoid keeping it in the glove compartment of a car.

By following these guidelines, you can ensure the safety and effectiveness of your insulin during storage and transportation.

Diabetes Educator Tip of the Month

Contributed by
Name: Ms. Sharleen Zacharia

MSc. Food Nutrition and Dietetics,
Certified Diabetes Educator

Targets for glucose management

Assessment of one's glucose status can be achieved using several methods, such as measuring the glycated hemoglobin (A1C), using finger-stick devices for blood glucose monitoring, or using time in range or mean glucose from continuous glucose monitoring (CGM).

1) Continuous glucose monitoring system (CGMS)

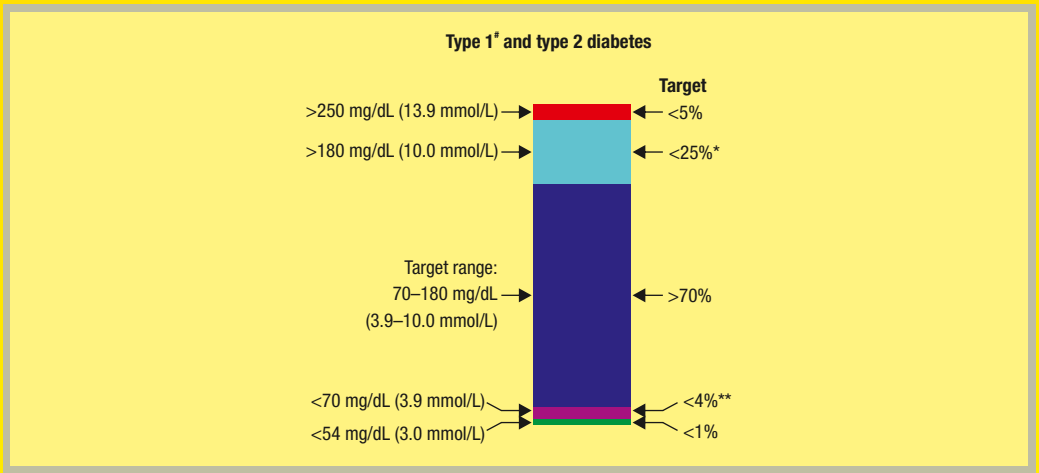

Figure 2: CGM-based targets for type 1 and type 2 diabetes

#For age <25 years, if the A1C goal is 7.5%, then set TIR target to approximately 60%.
*Includes percentage of values >250 mg/dL (13.9 mmol/L); **Includes percentage of values <54 mg/dL (3.0 mmol/L)
Abbreviations: CGM: Continuous glucose monitoring; A1C: Glycated hemoglobin; TIR: Time in range

2) Summary of glycemic recommendations for nonpregnant adults with diabetes (American Diabetes Association [ADA] 2024)

A1c	<7.0%
Preprandial capillary plasma glucose	80–130 mg/dL
Peak postprandial capillary plasma glucose (post 2 hours of meal)	<180 mg/dL

Resource:

- American Diabetes Association Professional Practice Committee. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes-2024. *Diabetes Care.* 2024;47(Suppl 1):S111-S125. doi:10.2337/dc24-S006.

Dia-Games

Find the odd one out

1. Syringe, vial, cartridge, plunger
2. Hybrid closed-loop insulin pump, insulin pens, continuous glucose monitoring system (CGMS), insulin syringe
3. Metformin, sulfonylurea, glargine, dipeptidyl peptidase-4 (DPP-4) inhibitor
4. Bariatric surgery, physical activity, dietary modification, cessation of smoking
5. Wearable technology, diet therapy, cell replacement therapies, immunological therapies
6. Fasting plasma glucose, glycated hemoglobin (HbA1c), urine ketones, body mass index

Answers
1.Cartridge
2.Continuous glucose monitoring system (CGMS)
3.Glargine
4.Bariatric surgery
5.Diet therapy
6.Body mass index

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Metformin Hydrochloride 850 mg SR + Glimepiride 2 mg

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Abridged Prescribing Information

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets **Indication:** For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycaemic control. **Dosage and Administration:** The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed. **Adverse Reactions:** For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia. Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders. **Warnings and Precautions:** For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis: In such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. **Contraindications:** Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR<30ml/min). In pregnant women. In lactating women.Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock); hepatic insufficiency; acute alcohol intoxication; alcoholism. **Use in a special population:** Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Additional information is available on request.

Last updated: March 13, 2023

In case of any adverse events, kindly contact: pv@usv.in For the use of registered medical practitioner, hospital or laboratory.

USV Private Limited Corvette Team

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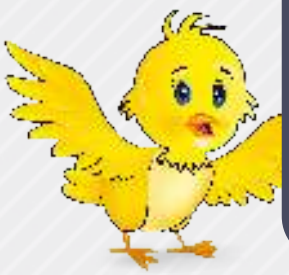

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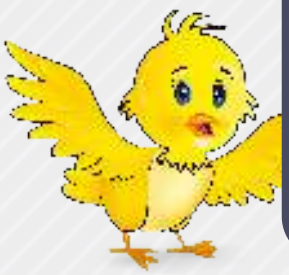

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NOTES

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