International Journal of Health Sciences and Research
Vol.13; Issue: 3; March 2023
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Technological and Therapeutic Approaches to Type 2 Diabetes Management

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DOI: https://doi.org/10.52403/ijhsr.20230320

ABSTRACT

There is an increasing burden of cardiovascular and microvascular complications associated with type 2 diabetes throughout the world. Efforts are made to enhance the quality of life and reduce complications caused by the condition. In this regard, improved glucose control remains a crucial factor. Type 2 diabetics' hyperglycaemia has been managed with important therapeutic advances in recent years. There are several drugs that can be used to control diabetes, including dipeptidylpeptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium glucose transporter-2 inhibitors. In addition to their antihyperglycaemic properties. There appear to be some specific benefits associated with these two classes in terms of cardiovascular and renal health. Insulin therapy is often necessary in many cases with progressing diabetes due to insulin deficiency and hyperglycaemia. Patients with diabetes, as well as their healthcare professionals, are at an increased risk for developing complications as a result of poor glycaemic control due to fear of hypoglycemia, poor understanding of treatment regimens, and lack of engagement with their treatments as a consequence of their clinical need for insulin therapy and their healthcare professionals' hesitation to intensify treatment with insulin. Various diabetes technologies, including dosing advisors, continuous glucose monitoring systems, insulin pumps, and automated insulin delivery systems, are being developed to make life easier for diabetics. These advances are also providing benefits to those with T2D, who face similar challenges in meeting recommended glycaemic standards. The purpose of this review is to examine new therapeutic agents and advanced technology for managing glucose levels in patients with type 2 diabetes. These technologies should be made available to people with T2D in order to reduce the effects of inadequate disease management in this population.

Keywords: type 2 diabetes, T2D, metabolic disorders, Type 2 diabetics' hyperglycaemia

INTRODUCTION

Diabetes is considered to be one of the fastest-growing metabolic disorders affecting most of the world's population. In 2017, it was estimated that almost 451 million people worldwide had diabetes, and by 2045, almost 693 million people could have diabetes [(1)]. According to estimates, India has the highest number of diabetics in the Southeast Asian region with 74 million people affected with the disease. Age-adjusted prevalence of diabetes in this age group is 9.8%, and premature mortality in this age group is 50.7% [(2)]. According to a cross-sectional study conducted by Indian Council of Medical Research-India Diabetes (ICMR-INDIAB), diabetes prevalence was 7.3% across 15 Indian states [(3)]. There have been significant improvements in type 2 diabetes (T2D) management guidelines over the past decade from a one-size-fits-all approach toward patient-centered care [4-7].

In the context of cardiovascular risk reduction, two landmark diabetes trials have provided evidence that this treatment is best achieved through a balance between glycemic control's benefits and its potential risks. Lifestyle changes, blood pressure (BP) control, and lipid control are all part of controlling cardiovascular risk.

Strict glycemic control, particularly in patients with long-standing T2D, may increase the risk of hypoglycemia, resulting in decreased quality of life and possibly increased cardiovascular risk, emphasising the importance of drug classes with low hypoglycemia risk. While lowering blood sugar slows the development and progression of microvascular complications, the impact of lowering blood glucose levels on cardiovascular-renal health problems is much more modest and manifests over a much longer period of time, highlighting the significance of drug classes with cardiovascular renal benefit. Although the idea of personalization is appealing, many healthcare professionals are faced with the challenge of how to implement this strategy in medical care, particularly when multiple drugs are recommended. Metformin is unquestionably the preferred and most widely used first-line pharmacotherapy for managing hyperglycemia in T2D. However, the American Diabetes Association (ADA) and European Association for the Study of Diabetes currently recommend the use of six different drug classes as part of combination therapy in addition to metformin: sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), dipeptidyl peptidase 4 inhibitors (DPP-4is), sulfonylureas, thiazolidinediones. Furthermore, technological advancements play an important role in diabetes management. It allows systems to record glucose readings throughout the day and detect glucose level trends.

Instructions for therapeutic management:

The ADA-EASD 2023 Summary Report recommends adopting person-centered care principles and approaches, including guarantee quality preferences and characteristics to determine personalized treatment goals and strategies, for the strategic approach of diabetes and its complications. Strategies that address glycemic variability, end-organ protection, comorbidities, and the use of newer technologies to monitor and start using newer anti-diabetic medications that favour weight loss and have positive effects on the kidneys and cardiovascular systems.

Innovations in pharmacology:

In the last two decades, there have been a significant increase in the number of therapeutic agents that are available for the management of hyperglycemia in T2D. In 2018, the US Food and Drug Advisory Committee ordered that cardiovascular outcome trials (CVOTs) be used to test the safety of all new antihyperglycemic medications (8). This was in response to worries about the use of rosiglitazone, an antihyperglycemic medication that, despite being effective, appeared to increase cardiovascular events in some patients (9). Heart failure (hHf), a frequent complication of T2D that raises mortality rates, is also included, typically as a secondary end point. Recent times, there has been change in the emphasis of trials that look specifically at renal outcomes.

Glucagon-like peptide-1 (GLP-1) agonists:

The L-cells of the small intestine secrete GLP-1 in response to glucose consumption, a natural peptide involved in glucose homeostasis. It has a direct impact on postponing stomach emptying and resulting satiety because it increases pancreatic -cell insulin production, inhibits -cell glucagon release, and stimulates -cell insulin secretion (10). The incretin effect, which is compromised in T2D, is this (11). GLP1-RAs promote insulin secretion that is glucose-dependent. They successfully lower

HbA1c levels significantly without running the risk of hypoglycemia. GLP1-RAs promote lipid and blood pressure improvements as well as weight loss. Because the formations and the duration of action of GLP1-RAs vary, as well as the size and patient characteristics of the CVOTs encompassing such agents, inconsistent results can be drawn from the research.

The 3p-MACE associated with GLP1-RAs was reduced by 12% in a meta-analysis of the seven largest trials, including ELIXA (12), EXSCEL (13), LEADER (14), SUSTAIN-6 (15), REWIND (16), PIONEER-6 (17), and HARMONY (18), which included 5604 patients. There was no heterogeneity between patient subgroups (19). Due to lower rates of CV death (12%), fatal or nonfatal stroke (16%), and fatal or nonfatal MI (9%), this observation was made. Additionally, there was a decrease in hHF (9%), as well as all-cause mortality (12%), primarily due to albiglutide (18). Some agents are more effective than others; however, lixisenatide and exenatide have not shown this (12, 13). For all GLP1-RA, the composite renal outcome was decreased by 17%, primarily as a result of a decrease in new macroalbuminuria.

Because of their exceptional glucose-lowering, weight-lowering, and cardiovascular (CV) benefits, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have taken on a significant role in the management of diabetes. Despite benefits and recommendations from various clinical practise guidelines, their use in clinical practise was constrained due to the fact that they were injectable. To overcome the difficulties of peptide absorption in the acidic conditions of the stomach, oral semaglutide is a novel GLP-1RA with 94% similarity to human GLP-1 that is co-formulated with uptake enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). An extensive phase 3 clinical trial programme called Peptide Innovation for Early Diabetes Treatment (PIONEER) evaluated oral semaglutide, and the results showed that it had superior glucose and weight lowering effects to other treatments.

Semaglutide or other GLP-1RAs have a minimal bioavailability of 0.01% when taken orally (20,21) Proteolytic enzymes and low pH cause proteins and peptides, such as semaglutide, to break down. Additionally, because of their high molecular weight these cannot pass through the GI epithelium, resulting in low absorption. This results in decreased bioavailability and decreased absorption (21, 22).

The first oral GLP-1RA in the world is semaglutide. As seen in the PIONEER clinical trial programme, this molecule has demonstrated its role in all phases of diabetes and in addition to a variety of antidiabetic medications. Comparing oral semaglutide to sitagliptin, empagliflozin, and liraglutide also reveals a significant HbA1c reduction and weight reduction. It has shown to be as safe as other GLP-1RAs in terms of CV, with manageable GI AE (23).

Dipeptidyl peptidase 4 (*DPP-4*) *inhibitors:*

Native GLP-1's bioavailability is raised by DPP-4i (gliptins). They raise endogenous insulin and lower glucagon to improve glycemic control. In comparison to GLP1-RAs, they show less improvement in glycemic control (8–10 mmol/mol [0.8–1.0%]) but greater improvements in HbA1C. They have few side effects, no weight-related effects, and little risk of hypoglycemia (24). Their use has been associated with a slight rise in pancreatitis risk (25). All of the CVOTs investigating DPP-4i (TECOS [sitagliptin] (26), EXAMINE [alogliptin] (27), SAVOR-TIMI53 [saxagliptin] (28), VIVIDD [vildagliptin in ventricular dysfunction diabetes] (29) CARMELINA [linagliptin] (30)] have shown CV safety but no evidence of CV protection.

Regardless of renal function, linagliptin can be administered to patients with CKD at a standard dose. The only study to date examining kidney outcomes of DPP-4i in

patients with T2D at high cardiorenal risk is CARMELINA. Regardless of the severity of renal impairment, linagliptin did not cause the progression of renal disease, but it did show lower rates of albuminuria progression (HR 0.86) compared to placebo (31).

Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors:

As SGLT-2 is inhibited in the proximal convoluted tubule by SGLT-2i (gliflozins), glycosuria is encouraged. Weight loss of up to 5 kg results from improved glycemic control as a result of this (32). They have similar glycaemic efficacy to traditional therapies (33). As their action is dependent on GFR, their ability to lower blood sugar decreases as renal function deteriorates. When combined with metformin, the glycaemic lowering effects of dapagliflozin and canagliflozin are equivalent to those of glimepiride (34, 35). Regardless of the dosage, canagliflozin and empagliflozin reduce HbA1c levels more than sitagliptin does when combined with metformin (36, 37). In the absence of sulfonylureas or insulin, there is a minimal risk of hypoglycemia (32).

The results of a recent meta-analysis of three sizable CVOTs investigating the effects of empagliflozin (EMPA-REG) (38) canagliflozin (CANVAS-PROGRAM) (39) and dapagliflozin (DECLARE-TIMI 58 (40) on CV and renal outcomes showed benefits in all endpoints, the magnitude of which varied depending on the patient characteristics in which they were used. For all patients who suffered from atherosclerotic CVD, SGLT-2i resulted in an 11% decrease in the 3p-MACE (HR 0.86 (0.80 to 0.93) vs. HR 1.00 (0.87 to 1.16)). Canagliflozin reduced CV death by 13% and empagliflozin reduced CV death by 38%. Both subgroups of SGLT-2i showed no impact on stroke (41).

Among patients with T2D and albuminuric CKD in the CREDENCE study (42), 50.4% had a history of CVD. Each participant was already taking an ACE inhibitor. Canagliflozin reduced the likelihood of renal-specific composite ESKD, renal or CV death by 34% over a median follow-up of 2.62 years. There is no heterogeneity between the primary and secondary prevention groups. In primary prevention groups with T2D and CKD, canagliflozin is the only antihyperglycaemic drug that reduces cardio-renal outcomes. Furthermore, it demonstrated cardiorenal efficacy at all stages of chronic kidney disease (43).

Tirzepatide:

As the only dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist, tirzepatide, also referred to as a "twincretin," can significantly lower glycemic levels, improve insulin sensitivity, as well as reduce body weight by more than 20% and improve lipid metabolism. This brand-new anti-diabetic medication is a synthetic peptide analogue of the human GIP hormone with a C20 fatty-diacid portion attached that, through acylation technology, can bind to albumin to deliver a dose of the medication by subcutaneous injection once a week that is in line with its half-life of about five days. The US Food and Drug Administration granted approval for Eli Lilly's tirzepatide, marketed as Mounjaro, in May 2022. This led to the 'twincretin' era of highly considerable and alluring dual treatment interventions for diabetes and obesity (44), as well as innovative management of closely related cardiometabolic settings, that are the main reason for morbidity, impairment, and mortality around the world.

Compared to current medications, tirzepatide has a significantly higher rate of therapeutic success (45, 46). Semaglutide (47,48) and insulin degludec are inferior to it (47, 49). The three most significant advancements are the addition of a C-terminal sequential manner from exenatide to extend the C-terminus by three, conjugation of the fatty acid chain length to increase half-life (to 116.7 h), and modification of peptide backbone residues

to produce GIP receptor turn activates activity (50, 51). Additionally, hepatoprotection must be remembered (52). Tirazepatide's structural underpinnings and functional adaptability have been reported (53), and its physiological mechanisms in T2D have been described (54). Tirzepatide was compared to semaglutide and placebo in the human clinical trial (NCT03951753) with regard to the responses of T2D patients to blood sugar levels after a meal over a 28-week period. When compared to semaglutide and placebo, tirzepatide significantly improved the clamp disposition index. This resulted in a significant increase in insulin sensitivity and total insulin secretion rate for tirzepatide. When compared to placebo, tirzepatide was found to slow glucose excursions during meal tolerance testing. Thus, tirzepatide was discovered to be effective in the treatment of T2D. (54, 55).

A Technological Advancement:

For those who have T2D, maintaining glucose control is still difficult because, as the condition worsens, insulin deficiency and hyperglycemia frequently call for insulin therapy. It has been acknowledged that many individuals with a clinical need for insulin therapy, along with their healthcare providers, are hesitant to intensify their insulin therapy due to apprehension about hypoglycemia, a lack of understanding of recommended treatment plans, or apathy. As a result, they are more likely to experience complications from poor glycemic control.

Recent technological developments offer useful ways to simplify glucose monitoring and increase the precision and safety of insulin therapy (56). In order to improve outcomes, this should be used to encourage appropriate treatment intensification. The development of diabetes innovations over the last ten years, which include dosing advisors, continuous glucose monitoring systems, insulin pumps, and automated insulin delivery systems, has greatly improved the therapies available, especially for those requiring insulin.

A flash glucose monitor

Utilizing a factory calibrated 14-day flash glucose monitor, the FreeStyle Libre, is a novel method of glucose monitoring that has been around since 2016 (57). (Abbott Diabetes Care, CA, USA). The upper arm is used to insert a minutely recording device, a small circular sensor with a thin fibre inside. The device stores glucose values for 8 hours, so able to record a full day's worth of glucose level necessitates at least 3 scans per day at intervals of 8 hours. By scanning the sensor with a compact reader or a smartphone with "relatively close field communication" capabilities, an ambulatory glucose profile is generated (AGP),providing a quick, minimally invasive way to check your blood sugar and the capability to analyse trends and variability in your blood sugar levels throughout the day and night (58) Flash glucose monitoring is more expensive than SMBG 8.3 times per day in the UK, which is more frequently than the typical testing frequency seen in T2D patients (59).

A continuous glucose monitoring system:

Continuous glucose monitors (CGMs), which can be used to circumvent the drawbacks of flash glucose monitoring and provide regular, real-time data and notifications without the need to physically scan a sensor. With more evidence mounting for their use in T2D, their use has increased, especially among those with T1D. HbA1c measurements and SMBG have traditionally been the main tools for evaluating glycaemia in people with insulin-treated T2D, but these tools have drawbacks. HbA1c has been demonstrated to be unreliable in some populations (60) and offers no data on glucose variability, undetected hypoglycemia, or glucose patterns. As a result, it is anticipated that percentage of time in value recorded by CGM systems will replace HbA1c as the

selected metric for evaluating diabetes (61,62).

The implantable glucose monitoring system

Since its introduction in 2016, the first implantable CGM (Eversense, Senseonics Inc., Germantown, MD, USA) has been marketed. It consists of a small cylindrical sensor that a skilled individual inserts into the upper arm. This offers glucose information for up to 180 days in conjunction with a smartphone app and a portable transceiver positioned over the sensor (63). Three pivotal studies involving T2D patients were conducted to assess the safety and accuracy of the Eversense CGM. The results showed that the system provided accurate readings for the duration of the sensor life and had a better safety profile than conventional transcutaneous CGMs (64-66). For patients who find it difficult or unpleasant to undergo routine sensor changes, patients who want a sensor that will last for a longer period of time and is implantable, Patients with comorbidities to the standard CGM adhesives or patients who may benefit from 'on-body' alerts through the transmitter's vibrating system (63).

A delivery system for insulin

Pens for insulin

In T2D patients, insulin pens are the most popular insulin delivery device (67). The standard insulin pen uses a disposable needle and a cartridge to deliver subcutaneous insulin. Although this method of administering insulin is convenient, due to the requirement for manual recording of blood glucose readings and the absence of a connection to a digital ecosystem, it is challenging for medical practitioners and users to perceive glucose statuses or assess dosing adherence. Over the past ten years, designs for insulin pens have changed to include a memory function, caps, attachments, and ultimately "smart insulin pens" with the ability to track doses and upload data to online platforms. The insulin pen's "memory" feature, which saves and displays data on previous bolus timing and amount, is especially helpful for those who have cognitive impairment or who are less engaged in managing their diabetes because of the complexity of dosing schedules (68).

The insulin pumps

Since the 1970s, continuous subcutaneous insulin infusion (CSII), also known as insulin pump therapy, has been used to mimic physiological insulin delivery for diabetics. A steel or plastic cannula that is changed every 48 to 72 hours is used to inject rapid-acting insulin into subcutaneous tissue at pre-programmed rates from a refillable reservoir. People with diabetes are using insulin pumps more frequently now because they are more convenient, portable, and reliable. This is especially true of the paediatric T1D population (69)

The use of CSII for those with T2D is currently discouraged by NICE guidelines (70), and an ADA and EASD consensus statement from 2018 only briefly mentioned the limited role of insulin pumps in a small subset of T2D patients (71).

Glucose responsive insulin therapy:

With the help of glucose responsive insulin delivery, also known as "closed-loop" or "artificial pancreas" systems, the difficulty is possible to bypass insulin therapy to regulate glucose excursions in T2D. A control algorithm uses real-time glucose readings from a CGM device to calculate and guide the delivery of insulin by an insulin pump.

Low glucose suspends, which halts insulin delivery below a predetermined glucose threshold, and predictive low glucose suspend, which foresees impending hypoglycemia and halts insulin delivery beforehand, are earlier features of glucose responsive insulin delivery systems (72). The next stage of development was a "hybrid" closed-loop system that requires meal announcements and the user to initiate a pump-delivered meal bolus because post-prandial glycaemic excursions are

particularly difficult. For the remaining period between meals, the basal rate is automatically maintained.

CONCLUSION

The management of diabetes has been influenced by numerous therapeutic and technological developments and is still evolving. New treatment options are now available, allowing for more customised patient care that takes patient preference, cost, disease severity, and medication profile into account. Furthermore, technological advancements have shown improved glycemic control in diabetic patients. The management of diabetes and patient outcomes can be greatly enhanced by the effective blending of pharmacological therapy, lifestyle changes, and technology.

Declaration by Authors

Ethical Approval: Not Applicable

Acknowledgement: None

Source of Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Rekha Krishnan, Rashmi Subramanian, Raja Selvarajan. Technological and therapeutic approaches to type 2 diabetes management. *Int J Health Sci Res*. 2023; 13(3):202-211.
DOI: *https://doi.org/10.52403/ijhsr.20230320*

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