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Recent Advances in The Management of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder whose prevalence has increased over the past few decades. The high prevalence and substantial associated morbidity and mortality have spurred remarkable progress in its management in recent years. These advances include the current management guideline that has shifted from a glucocentric approach to a more patient-centered and personalized approach. Novel medications targeting various pathways of glucose regulation, referred to as the "ominous octet," have also been developed. Notably, the advent of incretin-based medicines, such as glucagon-like peptide one receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, has provided the opportunity for enhanced glycemic control and reduced hypoglycemic episodes by lowering glucose levels through diverse mechanisms. Additionally, insulin delivery, a longstanding pillar in diabetes management, has advanced by incorporating continuous glucose monitoring technology into insulin pumps. This integration has ushered in the era of automated insulin delivery, often called the "artificial pancreas," offering improved precision in glycemic control.

Furthermore, recent reports from sizeable cardiovascular outcome trials have shown cardiovascular risk reduction and glycemic control benefits in diabetes management. These findings have led to the recommendation of antidiabetic drugs like sodium-glucose co-transporter 2 (SGLT2) inhibitors and GLP-1RAs in diabetic patients with high cardiovascular risk. Some SGLT2 inhibitors and GLP-1RAs have also been approved in diabetic patients with chronic kidney disease who are on the peak tolerated ACEi/ARB therapy doses. This review will explore the recent noteworthy trends in diabetes management, encompassing lifestyle modifications, drugs currently in development, prospects, and evolving therapeutic strategies.

INTRODUCTION

Diabetes Mellitus is a group of metabolic disorders arising from deficiencies in the secretion of insulin hormone from the beta cells of the pancreas, or due to the resistance offered by target tissues to its actions.[1] The prevalence of Diabetes mellitus has been on the rise over the past few decades and substantial number of deaths have been recorded due to its complications. In 2019, nearly half a billion people (9.3% of adults aged 20-79 years) lived with diabetes worldwide. This estimate has been projected to reach 643 million (11.3%) in 2030, and 783 million (12.2%) in 2045.[2]

A major discovery in the management of diabetes mellitus (DM) was made in 1921 when Frederick Banting and Charles Best discovered insulin therapy for diabetes.[3] Since then, numerous medications have been identified and developed to effectively manage this condition. (Figure 1)

CURRENT DRUG TARGETS FOR DM

Numerous glucose-lowering agents target eight distinct groups of pathophysiological mechanisms, first referred to as the "Ominous Octet" by DeFronzo.[23] Within these mechanisms, the muscle, gastrointestinal tract, liver, fat cell, β-cell, α-cell, gastrointestinal tract, brain and kidney, each play pivotal roles in the development of glucose intolerance among individuals with type 2 diabetes.[23]

INSULIN AND ITS ANALOGUES

Since its discovery in 1921, Insulin therapy has remained a cornerstone in the treatment of diabetes and has evolved over time. Initially, the sources of insulin were of animal origin, but with the emergence of genetic engineering and modern biotechnology, recombinant DNA technology has become the

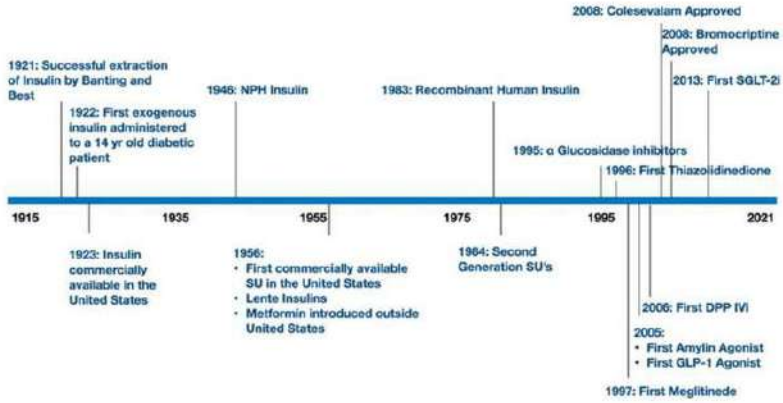

FIGURE 1: Historical dates of development of Diabetes Mellitus pharmacotherapy[22]

major means of insulin production (human insulin.).[4] Further improvement in insulin therapy saw the development of several insulin analogs. These include rapid-acting insulin, short-acting insulin, intermediate-acting insulin, premix insulin, and long-acting/basal insulin analogs.[4,5] Although insulin therapy is effective in the management of DM, it is fraught with several side effects and limitations (table 2), necessitating ongoing innovations to address these problems.[6,7]

MECHANISM OF ACTION OF INSULIN

Different somatic cells, majorly the liver, skeletal muscle, and white adipocytes, express insulin receptors to which insulin binds and the overall effect of insulin in these cells is to ensure a lowering of blood glucose by facilitating the transport of glucose into cells and glucose utilization by metabolizing tissues.[8]

Hypoglycemia has also been a key threat to the management of DM with deleterious effects on patients' quality of life. Hence, addressing hypoglycemia has also been a driving factor for the development of new insulin analogs and technologies over the years.[4]

The most recent form of insulin is the long-acting/ basal insulin; achieving balanced levels of glycemic control, with lower risks of hypoglycemia compared with the earlier forms.[4]

- **Insulin degludec:**

Insulin degludec is presently the longest-acting insulin analog employed in the treatment of type 2 DM. Several research studies have revealed that compared to other forms of long-acting insulin, such as insulin glargine and insulin detemir, insulin degludec exhibits the lowest risk of hypoglycemia. Furthermore, it can be administered with more flexibility and has sustained efficacy.[4,9]

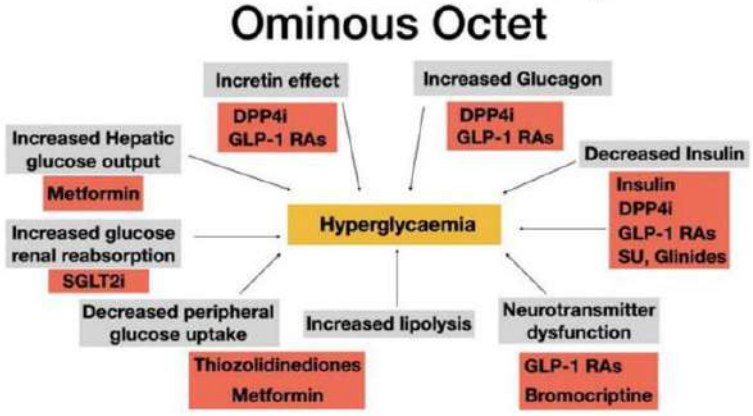

Figure 2: Ominous octets: drug targets for diabetes mellitus pharmacotherapy[22]

RECENT DEVELOPMENTS IN INSULIN THERAPY

In the earlier years of insulin therapy discovery, multiple insulin injections were administered to patients daily due to the short duration of action of the insulin[5] Each evolution of insulin therefore seeks to create a longer duration of activity and ultimately reduce the number of injections required.

- **Pre-mix insulin**

Regular insulin and isophane insulin represent the most commonly used premix combination worldwide, whereas theoretically, degludec-aspart is considered the most advanced combination.[22]

- **Insulin delivery pumps**

Insulin may be injected directly into the subcutaneous tissue or via Other newer insulin delivery systems including

INSULIN	ONSET OF ACTION	PEAK EFFECT	DURATION OF ACTION	EXAMPLES
Rapid-acting Insulin	15-30min	30-90min	4-5h	Lispro, Aspart
Short-acting Insulin	0.5-1h	2-4h	6-8h	Actrapid, Humulin, Neutral
Intermediate Insulin	1-2h	6-10h	10-16h	NPH (Neutral Protamine Hagedorn), LENTE
Long-acting Insulin	2h	6-20h	Up to 42h	Glargine, Detemir, Degludec

Table 1: types of insulin[5]

insulin jets, inhalational insulins, insulin pens, buccal insulins, rectal insulins, transdermal insulins, oral insulins and ocular insulins.[26]

These pumps have been integral in facilitating intensive insulin regimen in DM patients. lately, continuous glucose monitors have been integrated with insulin pumps to enable the automation of the insulin delivery process, often referred to as the 'artificial pancreas.' The United States' FDA has approved two such pumps (Medtronic and Tandem), and a third "do-it-yourself" option is currently in development.[22]

Drugs that were recently introduced in the management of diabetes: incretin mimetics, SGLT-2 inhibitors

INCRETIN MIMETICS

Incretin-based drugs have become a captivating focus for researchers and the pharmaceutical industry following the clarification of the incretin-insulin pathway. This category of medications includes glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors.[10,11] GLP-1 is a very active incretin hormone which has the ability to reduce the blood glucose via various mechanisms and acts at almost all the levels of the ominous octet as indicated in Figure 2.[12,13]

However, GLP-1 is rapidly metabolized after about 1-2 minutes by dipeptidyl peptide – IV (DPP – IV) enzymes. Hence, analogues of GLP-1 were made to be more stable to DPP-IV. Examples of GLP-1 analogues are; Exenatide, dulaglutide, Lixisenatide, albiglutide, and semaglutide [14]

Presently, GLP-1 receptor agonists (GLP-1RAs) are typically administered via subcutaneous injection. They have demonstrated effective results when used in combination with metformin and insulin. Additionally, they may potentially delay the need for insulin therapy in certain advanced stages of type 2 diabetes.[11] However, there have been reports of positive results of the use of GLP-1RA as supportive therapy with insulin in patients with T1DM. Results of some randomized studies also show reductions in hypoglycemic events, bolus and total insulin dose, as well as body weight after an adjunctive therapy of GLP-1RA with insulin in patients with T1DM.[13]

DPP-4 inhibitors potentiate the natural incretin effect by slowing down their metabolism. Examples include; sitagliptin, saxagliptin, linagliptin, vildagliptin, Alogliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin and Omarigliptin comprising a separate oral hypoglycaemic class, the "gliptines".[14,26]

DPP-IV inhibitors are commonly used as second line management of type 2 diabetes, however, there has been increasing attempts to their use in type 1 DM therapy. The results of some research on laboratory animals have proven that DPP-IV inhibitors have protective effects on the development of diabetic kidney disease in mice with type 1 DM. It also led to an improvement in the vascular endothelial function of STZ-induced diabetic rats. Research is also ongoing on their usage in humans with type 1 DM.[13]

Anti-hyperglycaemic agent	Advantages	Disadvantages
Insulin		weight gain, lipodystrophy, angioedema, urticaria, cancer cell proliferation, and severe/nocturnal hypoglycemia
Sulfonylurea (shorter-acting agents preferred)	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Thiazolidinedione	Improved lipid profile and potential decrease in MI (pioglitazone)	Fluid retention, heart failure, weight gain, bone fractures, potential increase in MI (rosiglitazone)
GLP-1 receptor agonist (daily to weekly injections)	Weight loss, reduction in MACE in patients with established CVD and potentially for those at high risk for CVD	Requires injection, frequent GI side effects, expensive
DPP-4	Weight neutral	Possible increased risk of heart failure with saxagliptin, expensive.
SGLT2 Inhibitors	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD, improved renal outcomes in patients with nephropathy	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, DKA.

TABLE 2: Overview of the advantages and disadvantages of some of the glucose lowering agents

SGLT2 INHIBITORS

The sodium-glucose cotransporter-2 (SGLT2) inhibitors can be referred to as the gliflozins; and include canagliflozin, empagliflozin and dapagliflozin amongst others.[11,15]

Since their introduction, the SGLT2 inhibitors have revolutionized the treatment approach to T2DM with an insulin-independent glucosuric function which makes them different from other hypoglycemic agents (figure 2).[11] This leads to the excretion of glucose in the urine, reduction of the glucose level in the blood and maintenance of other glycaemic parameters.[14]

They can be used as monotherapy or in conjunction with sulfonylurea, metformin or thiazolidinediones or as add on with insulin.[14] Also, a triple fixed-dose tablet made up of metformin + SGLT2 inhibitor + DPP-4 Inhibitor recently got the approval of the US-FDA.[11] Efforts have been made by pharmaceutical companies to develop dual SGLT2/SGLT1 inhibitors such as sotaglifozin but they have not yet gained FDA approval for the treatment of DM.[15] The four currently available SGLT2 inhibitors are ertugliflozin, empagliflozin , canagliflozin and dapagliflozin and all four are indicated for T2DM [17] In addition to the improvement of glucose metabolism, SGLT2 inhibitors have shown other benefits which has contributed to their wider use (Table 2).[16]

They may also be able to restore the circadian rhythm of mTOR activation thus having the potential to protect against cognitive impairment in patients with T2DM and other neuroprotective benefits.[16] They have also been receiving indications as adjunctive treatment to insulin in the treatment of T1DM.[11]

CARDIOVASCULAR OUTCOME TRIALS

Due to the excessive cardiovascular risk that is associated with T2DM and some claims that some antidiabetic drugs could increase this risk, the FDA has made it paramount that new antidiabetic drugs undergo cardiovascular trials which has led to the emergence of cardiovascular outcome trials (CVOT).[24]

Sequel to this, the cardiovascular safety of GLP-1RAs have been confirmed by the CVOTs. Also, some members of the class such as liraglutide, semaglutide and dulaglutide have shown impressive benefits to the MACE (major adverse cardiovascular events) and/or its various components including cardiovascular mortality.[11]

The results of an AMPLITUDE-O trial have also revealed that efpeglenatide, a new GLP-1RA in the pipeline, may prove to be a cardioprotective and renoprotective option with better medication adherence since it has the benefit of being a once monthly injection.[22] The cardiovascular safety of DPP-4 inhibitors including omarigliptin has been affirmed.[11]

CVOT trials of SGLT2i indicate that empagliflozin, canagliflozin and dapagliflozin are safe and are efficient in reducing MACE, hospitalization from heart failure and improving renal outcomes.[22] Dapagliflozin recently received FDA approval for the treatment of heart failure with or without T2DM. Thus far, only canagliflozin has received regulatory approval for use in patients with T2DM and CKD.[17]

GUIDELINES AND DECISION SUPPORT SYSTEMS

In 2022, The American Diabetes Association and the European Association for the Study of Diabetes reached a consensus which involved a holistic patient-centred and individualized approach to the management of T2DM. These areas of focus encompass an expanded emphasis on factors such as the healthcare system, social determinants of health, and behaviours related to physical activity, including sleep and weight management. The stipulated guidelines in the use of glucose-reducing medications in treating T2DM are as follows;

A. **Achieving and maintaining weight management and glycaemic goals**

- For the glycaemic management; Prioritizing the prevention of hypoglycemia is crucial for individuals at high risk.
- Efficacy of glucose lowering agents; VERY HIGH – high dose of dulaglutide, semaglutide, tirzepatide , insulin, oral combination, GLPIRA/insulin combination. HIGH –other GLPIRA, metformin, SGLT2i, sulfonylurea, TZD. INTERMEDIATE – DPP4i
- Weight management; The goals must be individualized. General lifestyle advice, medical nutrition therapy, physical activity, medications for weight loss or metabolic surgery. Also, the choice of glucose lowering agent here should have a high to very high efficacy in reducing both glucose levels and body weight.
- Efficacy for weight loss; VERY HIGH –semaglutide, tirzepatide. HIGH –dulaglutide, liraglutide. INTERMEDIATE –other GLP-1RAs, SGLT2i. NEUTRAL –DPP-4i, metformin

B. **GOAL; reduction of the cardiorenal risk in patients with T2DM**

- Patients with atherosclerotic cardiovascular disease and elevated cardiovascular risk factors should be offered either GLP-1RA or SGLT2i with documented CVD benefits. If the HBA1c remains above target, they can be combined.
- Patients with prior or ongoing heart failure with HFrEF or HFpEF should be offered SGLT2i with documented benefits in this condition
- In patients with CKD who are on the peak tolerated dose of ACEi/ARB, they should preferably be placed on SGLT2i or GLP-1RA with documented CVD benefits if SGLT2i is contraindicated or not tolerated.[25]

DRUGS IN DEVELOPMENT

- ***Glucokinase agonists***: Glucokinase acts a glucose sensor and triggers counter-regulatory responses following a change in glucose levels. This helps to restore normoglycemia. Dorzagliatin, a member of this class is currently being investigated in phase iii clinical trials, while AZD-1656, PB201 are at phase ii clinical trials. This class of drugs have a good safety and glucose-lowering profile. The side effects like hypoglycemia and abnormal serum triglyceride levels are however the challenges being faced by manufacturers.[18]
- ***Dual GIP and GLP-1RA:*** Tirzepatide is a novel drug in this class that is currently under review for marketing approval.[20]
- ***Resveratol (RES):*** This is one of the molecules from chinese herbal medicine. It is a polyphenol phytoalexin that has recently gained scientific interest for controlling blood sugar and its complications. This has been proposed to be due to the several actions of RES on cellular functions. (19)
- ***Imeglimin***: An investigational first-in-class novel oral agent for the treatment of T2DM that belongs to a class of oxidative phosphorylation blockers. Several pivotal phase iii trials that have been completed show evidence

of statistically significant glucose lowering and favourable safety profile.[22,21]

- ***Anti CD3 monoclonal antibody:*** teplizumab and otelixizumab have shown beneficial effects in T1DM patients and are being assessed to increase their safety and efficacy.[22]
- **New drug delivery systems under investigation as antidiabetics:** These include systems like liposome, niosome, nanomaterials, carbon nanotubes and transdermal patches.[22]

FUTURE PERSPECTIVES

Despite all the pharmacological advances in the management of DM, there are several future perspectives that will further revolutionalize the management and outcome of DM. These include the use of gene therapy to modify aberrant genes that are implicated in DM; beta cell regeneration therapies; stem cell therapy; small interfering RNA therapy; use of personalized treatment plans based on an individual's genetics, lifestyle and other factors; and the use of digital health tools.

In conclusion, these recent advancements and future prospects offer hope for improving the management of DM and substantially reducing the burden of this chronic condition.

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