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ADVANCES IN MEDICAL MANAGEMENT OF DIABETES

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Abstract:

Introduction: *Diabetes mellitus (DM) is a growing global epidemic that is causing a significant socioeconomic burden on nations. Since the traditional methods of treatment have significant side effects and have not addressed the disease's underlying causes, new strategies for managing diabetes mellitus are emerging quickly. Therefore, in order to create a clinical management plan that is strong, effective, and safe, the issues with each of these techniques must be resolved. The best possible metabolic management of blood pressure, glucose, and body weight is necessary, and improving diet, increasing physical activity, and reducing body weight all require the right information and assistance.*

Aim of the study: *This narrative review discusses various treatment plans, developments in the management of diabetes mellitus, and related challenges.*

Methodology: *The review is comprehensive research of PUBMED since year1995 to 2024.*

Conclusion: *Significant advancements in the treatment of diabetes mellitus have shown encouraging outcomes through the application of several therapeutic approaches, such as medical nutrition therapy, gene therapy, stem cell, nanotechnology, and lifestyle change. Nevertheless, there have been many difficulties in applying these techniques, such as optimizing them to guarantee the best possible blood pressure, cholesterol, and glucose regulation to reduce complications; enhancing patient adherence to pharmacological and lifestyle interventions; safety; ethical concerns; and developing an efficient delivery system, among other difficulties.*

Keywords – Diabetes mellitus, gene therapy, advance monitoring and drug delivery

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INTRODUCTION:

Diabetes mellitus is a chronic and progressive metabolic disorder of primarily carbohydrate metabolism that affects a substantially large population of humans. According to the International Diabetes Federation (IDF), around 537 million diabetics were living on Earth in 2021 which is 10.5% of the total world population. Unfortunately, the prevalence of diabetes is likely to increase in the future, and middle and low-income countries are affected the most. [1]

Diabetes is a complex medical disorder that manifests itself in a variety of ways and differs widely in how each individual reacts to therapy. It is frequently ineffective to follow the same treatment regimen for all patients, which can result in subpar outcomes and make blood sugar control difficult. These problems have led to the rise in popularity of personalized care, sometimes referred to as precision or individualized medicine. Personalized medicine aims to asses individual genetic information, lifestyle influences, and other health-related data to customize a treatment plan and plan precision-based interventions that maximize the effectiveness of treatment. [2]

Pathophysiology

Type 1 diabetes

It is an insulin-dependent diabetes that usually manifests in the early years of life. It is characterized by a deficiency of insulin due to the destruction of beta cells of the pancreas responsible for insulin production. The destruction of insulin-producing cells is due to autoimmune reactions in the body. The underlying genetic makeup of the individual and environmental factors play a role in the development of this disease. Patients are placed on a life-long insulin regimen. [3]

Type 2 diabetes

This is a non-insulin-dependent dependant diabetes that constitutes the majority of diabetes Mellitus cases across the world and typically occurs in later years of life. Normal glucose levels aren't maintained due to resistance among cells to insulin which leads to hyperglycemia. Lethargic lifestyle, obesity, junk food, and underlying genetic makeup influence the occurrence and progress of the disease. With an array of anti-diabetic medicines available each with a unique mechanism of action, it is important to tailor the regimen that is personalized to the patient to extract maximum benefits. [2]

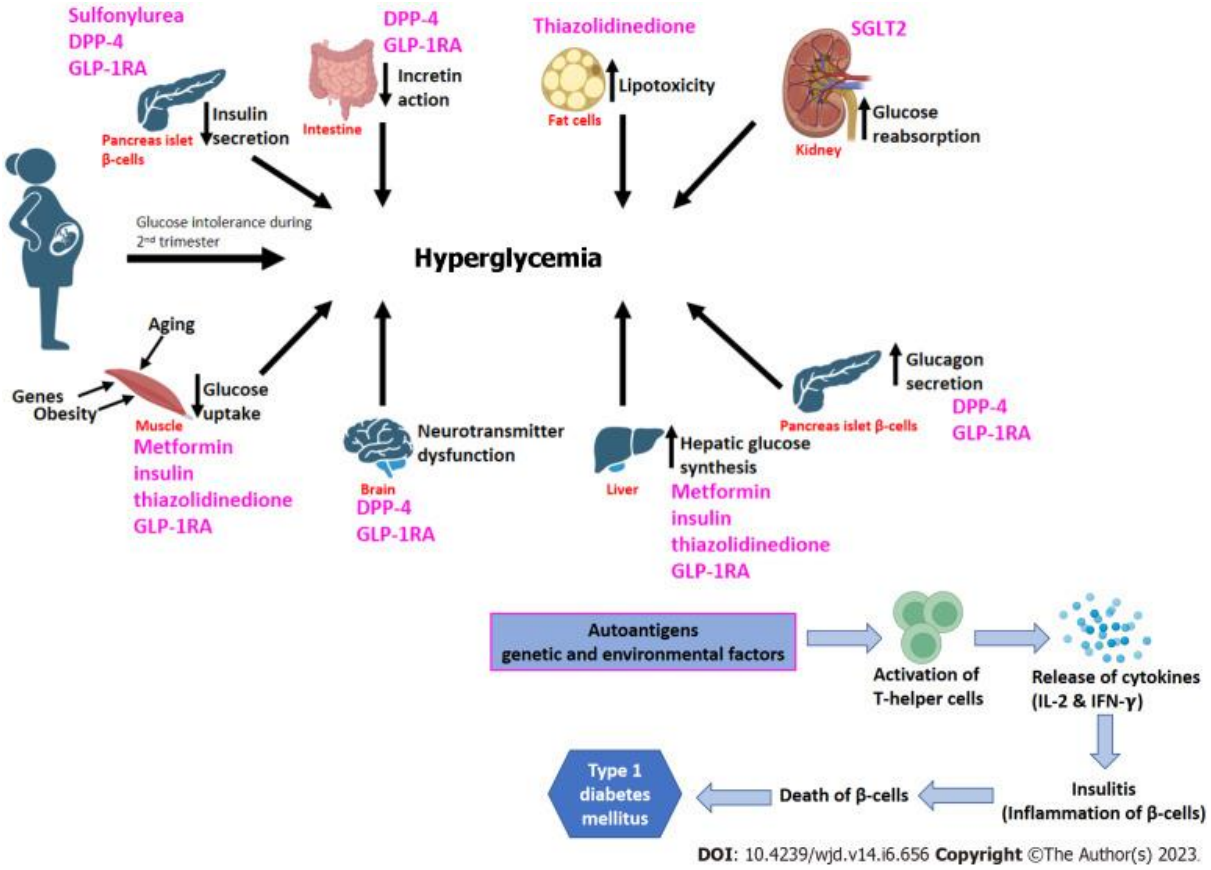

Figure: The complex pathogenesis of Gestational, Type 2, and Type 1 diabetes along with various pharmacological targets. [4]

Even when the outcome is hyperglycemia in diabetes Miletus, the underlying mechanism is quite complex and the interplay of various pathogonomic factors results in the disease. In type 1 diabetes, an innate trigger of autoimmune response may begin with a viral infection of B cells of the pancreas which causes infected cells to produce interferons that are recognized by macrophages. In later stages, T & B cells attack and destroy beta cells of the pancreas. Moreover, beta cells are also actively responsible for insulitis due to various stresses. [5]

The pathogenesis of type 2 diabetes involves an ominous octet of abnormalities. Decreased insulin secretion, reduced incretin action, amplified lipolysis, augmented glucose reabsorption, reduced glucose uptake, neurotransmitter dysfunction, increased hepatic glucose synthesis, and amplified glucagon secretion constitute the ominous octet. Various anti-diabetic drugs action different mechanisms of action and are prescribed based pathogenesis of diabetes type 2 in order to tailor the pharmacological management. [4]

Genetic studies

Type 2 diabetes in first-degree relatives is more likely to occur than in people of negative family history. Studies among monozygotic twins showed greater concordance rates than dizygotic twins suggesting a genetic component to diabetes. Kyvik et al in 1995 studied more than 20,000 Danish twins for type 1 diabetes and reported concordance rates of 0.53 and 0.11 for monozygotic and dizygotic twins respectively. The study also suggested not only greater risk concordance in monozygotic twins than zygotic twins but also higher risk compared to first-degree relatives. [6]

Genetic linkage studies have identified genes such as major histocompatibility complex (HLA) on chromosome 6 which may be involved in autoimmune reactions to beta cells of the pancreas in Type 1 diabetes. Similarly, calpain 10 genes (CAPN10) and TCF7L2 gene have been identified to be associated with Type 2 diabetes and influence insulin production, secretion, and glucose metabolism. In candidate gene-associated studies, genes such as IRS1, IRS2, PPARG, WFS1, and KCNJ11 play roles in insulin signaling pathways, glucose metabolism, and fat cell differentiation and are associated with type 2 diabetes. In genome-wide association studies, the underlying genetic pathways to diabetes were studied. UBASH3A (ubiquitin-associated and SH3 containing A), and CLEC16A genes were found to be involved in immune regulation and beta cell survival that related to type

1 diabetes. On the other hand, genes such as HHEX, SLC30A8, CDKN2A/2B, IGF2BP2, CDKAL1, and FTO involved in glucose metabolism, and regulation are associated with type 2 diabetes. [4]

Advances in Type 1 diabetes management

Early Diagnosis

Management of Type 1 diabetes must start with prevention, early diagnosis, and interventions. Autoantibodies to islet cells can be detected early on using simple assays. In unclear diagnosis, the C peptide test is used to evaluate beta cell function in suspected diabetics and it also helps to differentiate between type 1 and type 2 diabetes melitus. [7]

Advanced monitoring and drug delivery

A blood glucose monitoring system has traditionally been used for decades providing valuable data for both type 1 and type 2 diabetes mellitus. However, the constant pricking of a finger, patient compliance, and discontinuous data also present as drawbacks of the system. More recently it has been replaced by continuous glucose monitoring (CGM) which when implanted provides more continuous and real-time data on blood glucose levels. CGM evaluates interstitial glucose levels implanted inside the skin and displays it on a smartphone or watch. When CGM is integrated with an automated insulin pump, it becomes an artificial pancreas as it overtakes the function of beta cells. The pump delivers insulin using a small catheter placed under the skin. [7]

Figure: Showing wireless implanted monitoring device connected to a smart device and reciprocating implanted insulin pump to deliver precise insulin amounts. All are securely operated on a cloud database. [8]

Beta cell replacement therapy

Transplantation of beta cells or entire pancreas has been practiced to replace damaged or dead beta cells and restore euglycemic states without external insulin injections. Often, the pancreas is transplanted along with kidneys in patients with end-stage renal diseases. Such patients are kept on immune-suppressants and the survival rate of transplanted graft (simultaneous kidney and pancreas) is around 80% after 5 years. [9] There have been studies on the development of insulin-producing cells from stem cells either derived from the person or otherwise. The use of the patient's stem cells can avoid the need for immunosuppressants or stem cells can be designed that avoid immune surveillance. The number of cells required to achieve euglycemia and their survival still needs further inquiry. [10]

Type 2 Diabetes

Currently, infusing insulin-like substances and taking hypoglycemic medications orally are the two main treatment approaches for type 2 diabetes. These medications, despite having numerous negative effects, are essential in the treatment of type 2 diabetes. Since its discovery, insulin has been the mainstay for the treatment of uncontrolled insulin-deficient diabetes mellitus. It must be acknowledged that the injection of exogenous insulin is essential for survival because of the extreme absence of beta cells. Even with the advancements in understanding the causes, consequences, and persistence of diabetes mellitus, as well as the development of insulin and its analogues, there are still significant challenges in achieving precise glycemic control without adverse side effects like hypoglycemia and weight gain. Thus, this emphasizes even more how crucial it is to use adjuncts or alternate methods in addition to insulin. [11,12]

In 2022, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released a consensus report that called for more thorough and customized care for individuals with type 2 diabetes (T2DM), taking into

account their unique needs and preferences. Beyond diabetic management, clinical trials of GLP-1 receptor agonists (GLP-1 RA) and SGLT2 inhibitors (SGLT2i) demonstrate improved protection of the cardiorenal system's organs. They play a crucial part in the management of type 2 diabetes and greatly expand the range of available treatments.[13]

Sequential to early combination of drugs

In a sequential method, one oral glucose-lowering medicine is used initially, and if the treatment is ineffective, more medications are gradually introduced. The risk of complications rises with time, and many patients do not meet their glycemic objectives promptly, therefore this method has drawbacks. In order to meet glycemic objectives faster and lower the risk of complications, a more recent guideline is to give an early combination of two or more agents. The effect of early combination treatment for patients who were recently diagnosed with type 2 diabetes (T2DM) was investigated by the Vildagliptin Efficacy in combination with metformIn study (VERIFY), which demonstrated a much lower likelihood of initial treatment failure.[14]

Reduced use of metformin as a first-line drug

Due to its positive effects on weight, A1C, and cardiovascular mortality, metformin is recommended as first-line therapy. However, it is recommended that people with T2DM who have heart failure, chronic kidney disease, or established ASCVD—or who are at high risk of developing ASCVD also take a drug like an SGLT2i or GLP-1 RA, which has been shown to enhance cardiorenal outcomes. [15]

The effects of SGLT2i are insulin-independent, and hypoglycemia risk is reduced. SGLT-2 inhibitors, whether taken alone or in combination with other medications, lower HbA1c levels by 0.7%–1.0%. SGLT-2i has been demonstrated to encourage an average weight loss of 2-3 kg over a 6-month period. SGLT2i lowers the risk of cardiovascular events. Canagliflozin significantly lowers the risk of CV events and the progression of albuminuria for T2DM patients; however, this study shows a higher incidence of amputations and bone fractures.[16]

Regardless of whether a patient has diabetes or not, the DAPA-CKD trial assesses the impact of dapagliflozin on renal outcomes for patients with chronic kidney disease. The group receiving dapagliflozin medication has a considerably lower chance of meeting a pre-specified primary outcome than the group receiving a placebo.[17]

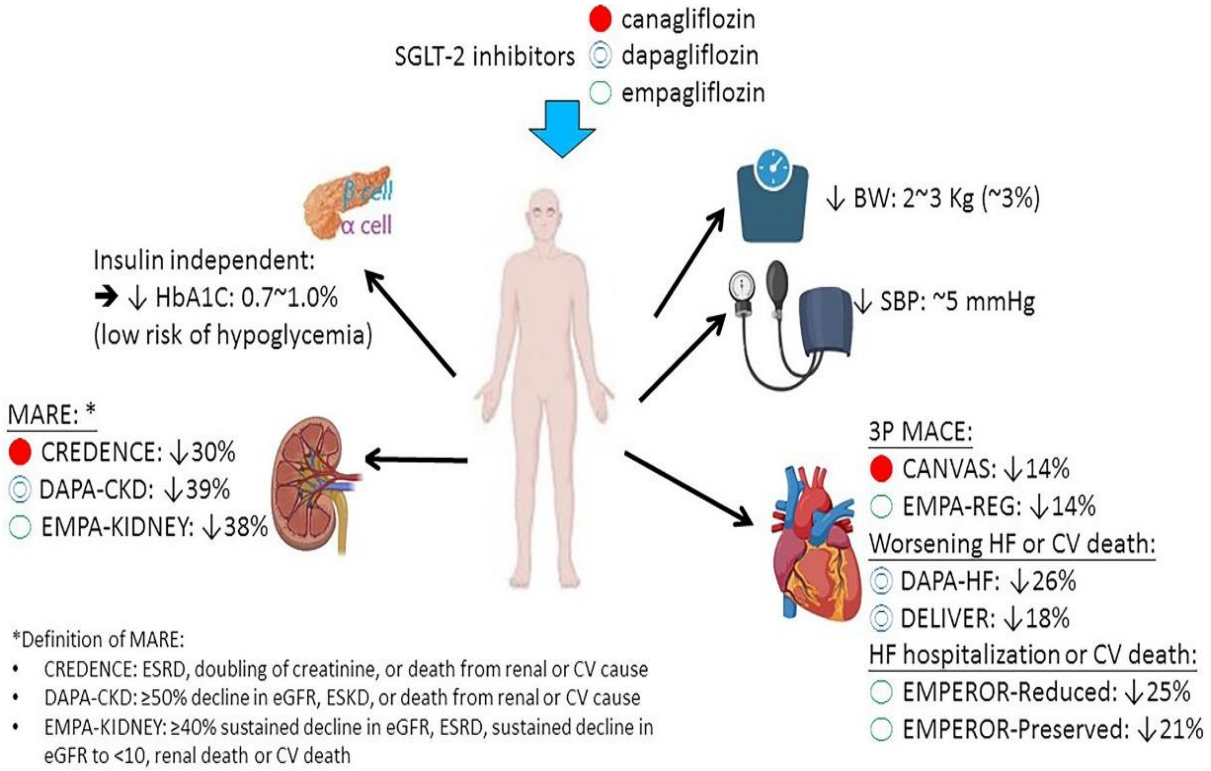

Figure: An overview of the metabolic impact and the historic SGLT-2 inhibitor trials.[18]

Gene Therapy

Gene therapy is a technique in which the external normal gene is included to treat the symptoms of a disease caused by a faulty gene. Due to the disease's strong genetic predisposition, numerous genes have been investigated as potential treatments for type 2 diabetes. Genetic linkage investigations have discovered approximately 75 distinct genetic loci associated with type 2 diabetes, as well as several new treatment targets. Unlike the frequency and development of diseases with limited impacts, genetic loci may have a significant influence on treatment responsiveness. There are numerous genetic loci that may be targeted with T2DM gene therapy.[19]

Novel Agents that are in Development

Amylin/GLP-1 dual receptor agonists – In response to dietary intake, beta cells release amylin, a pancreatic islet cell hormone, along with insulin. It slows down the emptying of the stomach and reduces postprandial glucagon. Weekly subcutaneous administration of cagrilintide, a long-acting analogue of amylin, is used both as monotherapy and in conjunction with the long-acting GLP-1 RA semaglutide.[20]

GIP/glucagon/GLP-1 triple receptor agonists – Glucagon is a 29-amino-acid peptide that accelerates glycogenolysis and gluconeogenesis. It is released by alpha cells of the pancreatic islets.[20]

Oral non-peptide glucagon-like peptide-1 (GLP-1) receptor agonist - T2DM is managed using orforglipron, a small drug belonging to the non-peptide GLP1-receptor agonist class. On orforglipron, HbA1c changes on average.[20]

Weekly basal insulin analog - Novel anti-diabetic medications lead to significant weight loss and organ protection; however, the primary objective in the management of type 2 diabetes is glucose control. For people with type 2 diabetes, insulin is crucial in regulating blood glucose, which is difficult to manage with traditional antidiabetic medications. Compared to previous-generation insulins, current basal insulin formulations are more effective and associated with a lower risk of hypoglycemia; however, poor adherence to daily dose is frequently observed, which is linked to poor glycemic control. Insulin icodec is an analogue of insulin that has been acylated with a side chain containing a C20 fatty acid. This acylation allows for robust and reversible binding to albumin, which in turn results in decreased clearance of the insulin receptor and decreased affinity for the insulin receptor.[22]

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