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CURRENT DEVELOPMENTS IN THERAPEUTIC STRATEGIES FOR THE MANAGEMENT OF DIABETES: AN EXTENSIVE REVIEW

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Abstract:

Diabetes is a prime example of a rising global epidemic that is posing a severe social and economic threat to all nations. Notwithstanding advancements in science, enhanced healthcare infrastructure, and higher rates of literacy, the illness still affects many people, particularly in middle-class and lower-income nations. Current trends point to an increase in premature mortality, which is a serious threat to global development. Newer generation drugs such as sulfonylureas (K_{ATP} Channel Blockers), Biguanide (AMP_K activator), α - glucosidase inhibitors, with notable efficacy in lowering hyperglycemia have been developed as a result of scientific and technological advancements. Novel therapeutic classes such as incretin mimetics, amylin analogues, GIP analogs, peroxisome proliferator activated receptors, and dipeptidyl peptidase-4 inhibitors have been developed as a result of recent advances in drug discovery techniques. These compounds may find application in the treatment of diabetes.

Keywords: Sulfonylureas ((K_{ATP} Channel Blockers), Biguanide (AMP_K activator), α - glucosidase inhibitors.

Introduction:

Diabetes mellitus (DM) is a long-standing, complicated, and non-transmissible endocrine ailment that is growing rapidly and has posed clinical challenges globally, often linked with threats related to complicated metabolic development in patients. It is marked by elevated glucose and lipids in the blood as well as oxidative stress, which culminate in chronic complications involving diverse organs, mainly the kidneys, eyes, nerves, and blood vessels, among others, in the body. As reported by World Health

Organization (WHO), DM is an outbreak prone to high malaise and death. Globally, approximately 387 million persons are affected by this disorder and it is estimated to be more than 640 million by 2040 [1]. According to a report in 2017 by International Diabetes Federation (IDF), 425 million persons suffer from diabetes mellitus out of which more than 90 percent are adults and 352 million had impaired glucose tolerance (IGT) [2]. In individuals suffering from type II diabetes mellitus (T2DM), hyperglycemia is not the only characteristic; it also involves multiple complications such as kidney failure, blindness, heart attack, stroke, and amputations of the lower limb [3]. Mounting evidence obtained from epidemiological studies has shown that T2DM is an ailment with numerous causes associated with both polygenic and various environmental factors [4]. T2DM is thus too complicated to cure due to genetic polymorphism and other numerous risk factors.

Despite the fact that most cases are a result of obesity-linked T2DM, the annual prevalence of T1DM is on the rise [5]. It has been reported that about 10 percent of people suffering from diabetes have T1DM. However, the two forms are linked with a prolonged risk of circulatory system complexities [6] and the threat of lowered blood glucose. Ample proof suggests that normoglycemia accomplishment will mitigate the risk of complications linked with DM [7]. However, hypoglycemia occurrences limit the attainment of near normoglycemia in subjects with T1DM. Diabetic individuals who are not aware of their hypoglycemic status are vulnerable to T1DM which then limits them from the attainment of the needed glycemic control. Globally, DM health centers have several individuals with T1DM who have recurrent low blood glucose and the idea of hypoglycemic unconsciousness poses critical clinical challenges. Providentially, manyfavorable and interesting gain ground exist in the perspective for subjects with the problemof DM, including gene therapy, as reported by Bosch and colleagues [8].

Currently, the main therapeutic regimens for T2DM are injection of insulin-like agents and oral administration of hypoglycaemic agents. However, these agents play crucial functions in T2DM treatment but are laden with side effects [9, 10]. Insulin has taken the centerpiece for the management of unrestrained insulin-deficient DM since its invention [11]. Admittedly, due to the severe lack of beta cells, the injection of exogenous insulin is vital for survival. Notwithstanding the advances made in comprehending the etiology, effects, and continuance of DM, including the progress made in insulin development and its analogues, ensuring tight glycaemic modulation without negative side effects such as low blood glucose and gain in weight still poses significant problems [7,12,13]. Hence, this further accentuates the importance of alternative techniques or adjuncts to insulin [14]

Diabetes Classification:

Diabetes can be categorized into the following types based on the lack of insulin.

A. Type 1 Insulin – dependent diabetes mellitus/Juvenile onset mellitus:

Type 1 diabetes, also referred to as juvenile onset diabetes, affects 5–10% of patients and is caused by an autoimmune autoimmune response that destroys pancreatic cells at the cellular level. Although the illness can strike anyone at any age, it typically strikes children or young adults. A consistent supply of insulin injections is necessary to regulate blood glucose levels. The rate at which β cells degenerate varies; in infants and children, it deteriorates quickly, whereas in adults, it degenerates more slowly. Children and young adults can experience

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Vol. 5 No. 2 (2023)

symptoms similar to ketoacidosis, while others show mild fasting hyperglycemia that can develop into severe hyperglycemia or ketoacidosis in response to stress or infection [15]. Other autoimmune conditions like Grave's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, Hashimoto's thyroiditis, Addison's disease, and pernicious anemia are more common in these patients [16]. People with African and Asian ancestry are more likely to have this type of diabetes, which has a genetic pattern [16].

B. Type II Noninsulin-dependent diabetes mellitus (NIDDM):

This type of diabetes, which makes up 90–95% of cases, is also known as adult onset diabetes. Type 2 diabetes is on the rise due to major metabolic syndromes such as obesity, insulin resistance, and dyslipidemia [17]. This kind of diabetes is treated with dietary hypoglycemic oral medications. Disease onset is influenced by both loss of insulin secretion and insulin resistance. The most prevalent type of diabetes, type 2 diabetes mellitus, has a two- to four-fold increased risk of coronary heart disease and stroke in addition to being the fourth greatest cause of death in developed nations [18].

Diabetes and Nanotechnology:

The application of nanotechnology in diabetes treatment has brought new approaches to insulin delivery and glucose monitoring. Researchers have shown how glucose sensors and closed-loop insulin delivery strategies can improve diabetes treatment, making it more effective for both type 1 and type 2 diabetes [19]. A nanomedical device is a porous microcapsule that has shown promise as a drug delivery method. These pores are sufficiently small to permit the passage of larger immune system molecules like immunoglobulins and graft-borne virus particles, but they are sufficiently large to permit the passage of small molecules like oxygen, glucose, and insulin. Patients with diabetes may have microcapsules containing replacement islets of Langerhans cells—mostly derived from pigs—implanted under their skin. By doing this, the body's delicate feedback loop for controlling glucose may be momentarily restored, negating the need for strong immunosuppressant's that put patients at risk for infection [20]. The scalability of a nanoparticle is one of the main technological obstacles. Producing three-dimensional nanostructures is more difficult than producing standalone or two-dimensional layer-shaped nanosurfaces because the manufacturing processes are not yet standardized. The possibility of toxic or dangerous exposure to nanoparticles is another concern. There is growing concern regarding the possible negative effects of ingestion, skin absorption, or inhalation of engineered nanomaterials like carbon buckyballs and nanotubes [20]. Advanced type 1 and type 2 diabetes both depend on insulin, and the conventional insulin delivery methods included patient noncompliance, painful injection procedures, and infection risks. On the other hand, newer micro- and nanotechnologies have made insulin administration easier by controlling insulin delivery, which includes transdermal, pulmonary, nasal, and closed-loop delivery.

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Vol. 5 No. 2 (2023)

Statin Therapy: An Alternative Viewpoint:

Statins are characterized as 3-hydroxy-3-methylglutaryl coenzyme Inhibitors, which block the vital liver process that produces LDL cholesterol and consequently lower blood levels of it toleration and fewer negative effects, statins may result in myopathies and elevated liver enzyme levels in people with type 2 diabetes [43].

Stem Cell Technology: An Innovative Treatment Method:

The quest for a potential diabetes treatment has ultimately led to the exploration of several novel scientific fields, one of which is stem cell technology. It is well known that a pancreatic cell deficit leading to insufficient insulin secretion causes both type 1 and type 2 diabetes. The goals of the strategies should be to either improve the body cells' sensitivity to the action of insulin or eliminate the defects in the pancreatic N cell. While current strategies aimed at pancreas transplantation and islet cell replacement are limited due to a shortage of donor organs, stem cell replacement strategies provide a novel source [21]. Type 2 diabetes is brought on by abnormalities in the function of $\boldsymbol{t}$ cells combined with insulin resistance in peripheral organs, as opposed to type 1 diabetes, which is brought on by the immune system's destruction of pancreatic β cells [22]. Because mesenchymal stem cell (MSC) therapy suppresses the immune system, it has become a promising treatment option for type 1 diabetes. Because of their direct contact and ability to produce soluble markers, MSCs have been shown to exhibit immunomodulatory effects in both in vitro and in vivo settings [23–26]. MSCs possess the capacity to differentiate into various lineages of mesenchymal cells. Hematopoietic stem cells are multipotent stem cells with the ability to differentiate into every type of blood cell and the ability to modulate the immune system. Therefore, hematopoietic stem cell transplantation has shown to be a promising therapeutic, improving the function of beta cells in patients with type 1 diabetes who have just been diagnosed [27]. Subsequent research has shown that adult fibroblasts from type 1 diabetic patients can be reprogrammed with three transcription factors (OCT4, SOX2, and KLF4) to produce induced pluripotent stem (iPS) cells. Diabetes-induced pluripotent stem cells, or DiPS, are pluripotent cells with the capacity to develop into cells that produce insulin. Modeling type 1 disease and cell replacement therapies benefit from this [28].

Diabetes and Gene Therapy:

The 1970s saw a great medical revolution with the series of experiments that resulted in the cloning and expression of insulin in cultured cells. Gene therapy was then proposed as a potential treatment for diabetes. The most crucial part of the treatment, which also lessens the disease's complications, is controlling blood sugar levels. There are two ways to deliver genes during somatic gene therapy, which uses the body's somatic cells. The first, referred to as "ex vivo gene therapy," is defined as removing body tissues and inserting the therapeutic gene in vitro before reintroducing it into the body, whereas "in vivo gene therapy" entails inserting gene therapy

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Vol. 5 No. 2 (2023)

vectors directly into the the patients by local injection, subcutaneous, intravenous, or intrabronchial routes [29]. The goal of ex vivo therapy is to create cells that have CELL characteristics, such as the ability to produce insulin [30]. Moreover, this treatment has been used to produce β cells for transplantation. The process of surgically extracting the patient's tissue and reintroducing the genetically altered tissues into the patient's body, however, raises concerns [29]. Moreover, the autoimmune destruction of pancreatic N cells that synthesize insulin causes type 1 diabetes, and islet transplantation has been investigated as a potential treatment option. By creating insulin secretory non-β cells that are immune system-insensitive, insulin gene therapy replaces β cell function.

Nutrition Therapy for Medical Conditions:

With the goal of using nutrition therapy for the treatment of disorders and illnesses, medical nutrition therapy in the prevention and management of diabetes presents many advances in clinical research. The term "medical nutrition therapy" was first used by the American Diabetes Association in 1994. It consists of two phases: determining an individual's nutritional needs and providing treatment through nutrition therapy and counseling, respectively [31]. The goals of nutritional therapy for diabetes are to maintain ideal blood lipid levels, a healthy body weight, and a normal blood glucose range. In addition to an exercise program and suggested nutritional requirements based on the patient's abilities and health conditions, nutrition therapy as a treatment for diabetes depends on a number of factors, including the patient's age-based nutritional requirements and food preferences as well as other medical conditions [32]. Calorierequirementtomaintain for those who are moderately active, the ideal body weight is 30-35 kcal/kg per day; for those who are obese, it is 20-30 kcal/kg per day. If daily caloric intake is decreased by 500 calories, it is estimated that weight loss should occur gradually at the rate of 1 pound per week.As per the latest guidelines, the percentage of carbohydrates consumed by the patient is determined by their intake of fat and protein. Popular low-carb/high-protein diets are hard to stick to over the long term, but they can be linked to initial weight loss and better glycemic control. Maintaining a protein intake of 10–20% of total calories, limiting total fat intake to <30% of total calories, adhering to a high-fiber diet (20–35 g/day of soluble and insoluble fiber), limiting sodium to 2400–3000 mg/day, limiting alcohol intake (≤2 drinks/day for men, ≤1 drink/day for women), and taking multivitamins are all recommended [32].

Sugar and Natural Goods:

Since ancient times, herbal remedies have been recommended in literature as a means of treating both insulin-dependent and noninsulin-dependent diabetes. Plants with anti-diabetic qualities could be used as a supplement to current treatments or as a potential source of novel hypoglycaemic substances. Natural remedies have been used for a variety of illnesses since the beginning of time and are still becoming more and more well-liked today. Diabetes has been documented in ancient literature since the Brahmi period and is mentioned in the Sushruta

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Samhita, an Ayurveda text written in the fourth and fifth centuries BC [33]. There have been two types of diabetes identified: one caused by genetics and the other by poor dietary choices [34]. The general public is growing increasingly reliant on herbal medicines due to their low cost and minimal adverse effects. Despite the fact that plant-based medications have long been used to treat illnesses all over the world, most herbs' mechanisms are still unknown and need to be standardized [35]. Numerous novel bioactive compounds derived from plants with hypoglycaemic properties exhibit antidiabetic activity comparable to, or occasionally even stronger than, established oral hypoglycaemic medications like daonil, tolbutamide, and chlorpropamide. Many other active ingredients derived from plants, though, lack sufficient characterization [36]. Grover et al. [37] proposed that plants with antidiabetic properties should be of great interest to the ethnobotanical community because many of them have demonstrated variable degrees of hypoglycaemic and antihyperglycemic activity, and they are known to have valuable medicinal properties in various parts of the body. Many plant species contain bioactive constituents that can be extracted and used directly as drugs, also known as pharmacological agents or lead compounds. These conventional methods may provide a natural key to unlock the mysteries of diabetic complications [38]. An important factor in a phytomolecule's ability to prevent diabetes is its chemical structure. According to Jung et al. [39], a number of plant species that are important sources of terpenoids, flavonoids, phenolic, coumarins, and other bioactive components have been shown to lower blood glucose levels. Many plants, such as Garlic etc.

Diabetes and Natural Products:

Since ancient times, herbal remedies have been recommended in literature as a means of treating both insulin-dependent and noninsulin-dependent diabetes. Plants with anti-diabetic qualities could be used as a supplement to current treatments or as a potential source of novel hypoglycemic substances. Natural remedies have been used for a variety of illnesses since the beginning of time and are still becoming more and more well-liked today. Diabetes has been documented in ancient literature since the Brahmic period and is mentioned in the Sushruta Samhita, an Ayurvedic text written in the fourth and fifth centuries BC [33]. There have been two types of diabetes identified: one caused by genetics and the other by poor dietary choices [33]. The general public is growing increasingly reliant on herbal medicines due to their low cost and minimal adverse effects. Despite the fact that plant-based medications have long been used to treat illnesses all over the world, most herbs' mechanisms are still unknown and need to be standardized [34]. Numerous novel bioactive compounds derived from plants with hypoglycemic properties exhibit antidiabetic activity comparable to, or occasionally even stronger than, established oral hypoglycemic medications like daonil, tolbutamide, and chlorpropamide. Many other active ingredients derived from plants, though, lack sufficient characterization [35,36]. Grover et al. [37] proposed that plants with antidiabetic properties should be of great interest to the ethnobotanical community because many of them have demonstrated variable degrees of hypoglycemic and antihyperglycemic activity, and they are known to have valuable medicinal properties in various parts of the body. Many plant species contain bioactive constituents that can

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Vol. 5 No. 2 (2023)

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Prospects for the Future:

With a global presence, diabetes continues to be one of the most difficult health issues of the twenty-first century. Diabetes is a significant public health issue, but there is good news: significant progress is being made in the diagnosis, treatment, and prevention of the disease. Patients with type 1 diabetes need to take insulin three to four times a day for the rest of their lives, and to prevent complications like retinopathy and cardiovascular disease risks, blood sugar levels need to be checked frequently. Although the demand for organ transplantation is greater than the supply, it is estimated that 1300 patients with type 1 diabetes receive a whole organ transplant—a pancreas—and are spared from needing insulin infusions. Rejection of a transplanted organ is another risk factor; as a result, the patient is given strong immunosuppressive medications, which can result in other serious illnesses [86]. Glycaemic control must be closely monitored in order to manage type 2 diabetes. Since it can result in a loss of glycaemic control, it is imperative to control the progressive deterioration of β cell function. While insulin and conventional medications work well, they are unable to correct the underlying glucoregulatory and metabolic dysfunctions. Diabetes is becoming a bigger threat every day, so aggressive, focused combinational therapy—especially incretin-based therapy and peptide analogs—is desperately needed. This could stop the development of type 2 diabetes and preserve and restore β cell function [87]. Clinical progress has been made in the areas of disease development, prevention, and treatment, but as of yet, no therapeutic approach has proven to be entirely effective. The search for a successful drug is not far off, as new technologies are transforming the options for treatment. The field of diabetes research has undergone a significant revolution thanks to the comprehensive study that identified the genes involved in the disease's development and the sequencing of entire genomes. The identification of faulty genes and mutations in an organism's genome has expanded thanks to the development of techniques like PCRs, DNA microarrays, and gene knockouts with silencing. The rising incidence of diabetes worldwide is putting a financial strain on each nation's economy. Diabetes can be treated, unlike some other diseases, and when properly managed, it can significantly lower the risk of complications like heart attacks, amputations, blindness, and kidney failure. It is still possible to find the ideal medication to treat diabetes with the continued research.

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Vol. 5 No. 2 (2023)