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TARGET TREATMENT IN DIABETIC AND MICROVASCULAR COMPLICATIONS: AN UPDATED REVIEW

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ABSTRACT: Diabetes Mellitus is the most common endocrine disorder, affecting a larger population of the world, which arises due to defective insulin secretion by beta cells in the pancreas or insulin resistance by peripheral tissues. As the disease progress, microvascular complications like nephropathy, neuropathy, retinopathy, and cardiovascular complications are observed, which the leading causes of death in diabetic patients. The drug treatment is required when the weight reduction, diet, and modification in lifestyle fails to maintain the normal blood glucose level. Though insulin and oral anti-diabetic drugs are clinically being used; the researchers have been focused on developing still better anti-diabetic drugs. There components like GLP-1, DPP-4, GPR119, GPR 40 and GPR 120, SGLT2, DGAT-1, 11 β-hydroxysteroid dehydrogenase, and Peroxisome proliferator influences/regulate the secretion, release, and uptake of insulin. The study of these targets would help to develop new anti diabetic drugs.

INTRODUCTION: Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century, and it is a major risk factor for cardiovascular diseases. Diabetes mellitus is a metabolic disorder characterized by hyper-glycemia, hyperlipemia, negative nitrogen balance and ketonemia resulting from irregularity in insulin secretion, insulin action or both. It is the oldest disease known to man. It is also referred to as Black Death since 14th century [1]. The expressions "Diabetes" and "Mellitus" are gotten from Greek. "Diabetes" specifies "a passer through; a siphon"; however, the "Mellitus" implies "sweet". It is felt that the Greeks named it so because of the over the top measures of pee delivered by diabetics pulled in flies and honey bees.

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The conventional method for diagnosing diabetes mellitus in old Chinese was by seeing whether ants are attracted to a person's urine or not. The most recent data from the International Diabetes Federation indicated that an estimated 415 million adults aged 20-79 years worldwide are diabetics, and the number will project to 642 million by 2040. Despite the high prevalence of diagnosed diabetes mellitus, as many as half of the people diagnosed with diabetes, mellitus is unaware of their disease. China, India, and the USA are the top three countries with largest number of people diagnosed with diabetes [2]. The WHO has predicted that with the aged people, children, and adolescents in both the developed and developing countries affected mostly with this disease. The incidence of type 2 diabetes is higher in males compared to females, maybe due to sex-related differences in sensitivity, obesity, and excess accumulation of fat and other causative factors like raised blood pressure or habits like smoking and alcohol consumption [3]. The WHO estimates that about 3.4 million people died from consequences of hyperglycemia in 2004.

80% of total diabetes deaths occur in low and middle income developed countries. Also, WHO assumes that diabetes will be 7th leading cause of fatality in 2030 [4].

Types of Diabetes Mellitus:

Type I (IDDM-Insulin Dependent DM, Juvenile onset DM): In this condition, the beta cells of the pancreas are partially or completely degenerate, which results in insufficient insulin secretion. It is also due to autoimmune disorder, which causes the destruction of beta cells by autoantibodies. Therefore, the type I diabetes patients depend on other sources of insulin for normal metabolism. This type is less common and has low genetic predisposition [5].

Type II (NIDDM-Non Insulin Dependent DM, Maturity onset DM): In this type, there will be the development of insulin resistance due to the progressive dysfunction of beta cells of the pancreas. The excess of hyperglycemic hormones (ex: glucagon), obesity, and hyperlipidemia are the chief contributors for insulin resistance [6]. It has a high degree of genetic predisposition. Among all Diabetic patients, about 90-95% are Type II diabetics, and it is most effective than other types [7].

Gestational Diabetes: It is temporary and appears during pregnancy, usually develops during the third trimester of pregnancy. It complicates about 7% of pregnancy, which accounts about 2,00,000 cases per annum. The recent study indicates that 18.9% of Gestational Diabetes cases are from India. The main contributors are the placental hormones, particularly human placental lactogen, progesterone cortisol, growth hormone and prolactin [8].

Complications of Diabetes Mellitus: Most of the complications of Diabetes mellitus are similar regardless of the type of diabetes. These complications are responsible for the morbidity and mortality associated with both type I and type II Diabetes Mellitus [9]. The complication of Diabetes increases with the severity of the disease [10]. Diabetic complications are categorized broadly into microvascular and macrovascular complications.

Micro-vascular Complications: These are diseases of small blood vessels that arise due to diabetes. The main microvascular complications are retinopathy, nephropathy, and neuropathy. These arise due to the thickening of the basement membrane in the capillaries and arterioles of blood vessels [11]. Hyperglycemia is the primary cause of microvascular complications.

In Diabetic retinopathy, friable and poor quality blood capillaries developed in the retina as well as macular edema and grown with the progression of the disease, which leads to loss of vision or blindness [12]. Retinopathy may start to develop as early as 7 years before the diagnosis in patients with type 2 diabetes mellitus [13]. It is a leading cause of blindness in the USA. There are two types of diabetic retinopathy. In background retinopathy, there is occlusion of small blood vessels in retina with the formation of microaneurysms in the capillary wall, whereas the proliferative retinopathy is characterized by total occlusion of small blood vessels in the retina leading to the destruction of retinal capillaries [14].

Diabetic Nephropathy is a leading cause of renal failure in diabetes. It is the major cause of kidney failure worldwide. The structural abnormalities of nephropathy are, hypertrophy of kidney, increased glomerular basement thickness, nodular and diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis that cause increased glomerular filtration rate with intra glomerular hypertension, proteinuria and loss of renal function [15]. These sequences are similar in both type 1 and type 2 diabetes.

Diabetic Neuropathy is a life-threatening complication involves both peripheral and autonomic nervous system, affecting nearly half of the diabetic patients. Chronic hyperglycemia over a period of years is the primary cause for neuropathy in diabetes, as it causes accumulation of polyols in nerves [16]. In hyperglycemic neurons the sensory neuron mitochondria are the source of production of reactive oxygen species which can damage their DNA and membranes; impair cell function leading to nerve degeneration [17]. In this, the patients complain of burning, irritating, and stimulatory pain. The sensory-motor neuropathy affects the distal portion of the nerves, especially the lower extremities, whereas autonomic neuropathy affects almost every organ and system of the body [18]. Glycemic control and tissue transplantation can be used to delay or prevent the development of neuropathy.

Macro-vascular Complications of Diabetes Mellitus: Macro-vascular complications arise due to atherosclerotic changes in larger blood vessels. This means that the central mechanism of micro-vascular complications is atherosclerosis. It involves the chronic inflammation and injury to the arterial wall in the peripheral and coronary vascular system resulting in accumulation and rupture of oxidized LDL particles in the endothelial wall of the arteries [8]. The macrovascular complications associated with DM are coronary artery disease, cerebral and peripheral vascular disease.

Coronary Artery Disease (CAD) is a leading cause of death in most of the individuals with type 2 diabetes. It is asymptomatic, usually leads to the sudden death of patient [19]. The myocardial infarction is the main CAD, and it accounts for about 60% of all diabetes-associated mortality. Lack of early warning signs makes it difficult to treat. Cerebral Vascular Disease arises due to atherosclerotic changes in cerebral blood vessels. It involves the formation of embolus in a vascular system, which blocks the blood flow to the cerebral region which causes transient ischemic attack and stroke [19]. Recovery from stroke is difficult in diabetic patients because of the high blood glucose levels.

Peripheral Vascular Disease is referred to as Lower Extremity Arterial Disease (LEAD), occurs due to atherosclerosis in larger blood vessels of lower extremities of the body such as legs and feet. It is clinically identified by the absence of a peripheral pulse in the lower extremities. It is responsible for gangrene in diabetic patients [20].

Management of Diabetes Mellitus: DM is a chronic disease, in which there is no definite cure, except in a very precise situation. Management depends on the maintenance of normal blood glucose levels, which can be achieved by a healthy diet, weight loss, regular exercise, lifestyle modification, and the use of appropriate drugs.

In spite of great advancement in the development of modern medicines and therapeutic approaches for the treatment of DM, search for still better, safe and effective remedies find enough scope in recent years. Researchers in different disciplines are working to find out new targets and strategies which can regulate the blood glucose level for the treatment of Diabetes Mellitus. Here, we have made an attempt to summarize the approaches and targets used for the treatment of Diabetes Mellitus.

1. Glucagon-Like Peptide (GLP-1): GLP-1 is a 30-31 amino acid long peptide hormone getting from tissue explicit posttranslational preparing of proglucagon peptide. GLP-1 is bundled in secretory granules and emitted to hepatic entry framework by intestinal L-cells upon stimulation by factors like nutrient, neural, and endocrine. Once secreted GLP-1 is rapidly degraded by proteolytic enzyme Dipeptidyl Peptidase-4 (DPP-4). Hence, the half-life is only 2 minutes, and only 10-15% of GLP-1 reaches the circulation intact [21].

GLP-1 exhibit several physiological actions, making it a subject of intensive investigation as a potential target for the treatment of Diabetes Mellitus. It has the ability to promote insulin secretion in a glucose-dependent manner and decreases glucagon secretion. The GLP-1 binds to the GLP-1 receptors on the pancreatic cells, the adenylate cyclase is activated, which increases the production of cAMP. With subsequent activation of secondary pathways, causes elevated levels of cytosolic calcium ions that enhance the exocytosis of insulin-containing granules. Also, GLP-1 promotes the proliferation of beta cells, which increases the beta-cell mass [22]. As both type 1 and type 2 diabetes is associated with a reduction of functional beta cells, the GLP-1 would be an interesting target for diabetes treatment. Since the GLP-1 is rapidly degraded, GLP-1 agonists and DPP-4 inhibitors have been developed for clinical use. Some examples of GLP-1 agonists are Exenatide [23, 24], Liraglutide [25, 26], Dulaglutide [27, 28], and Semaglutide [29, 30].

2. DPP-4 (Dipeptidyl Peptise-4): It is also known as Adenosine Deaminase Complexing Protein 2 or CD 26 is a protein that is encoded by the DPP4 gene [31]. DPP-4 is known to separate a wide range of substrates, including vasoactive peptides, chemokines, neuropeptides, and growth factors. DPP-4 plays a major role in glucose metabolism, responsible for the degradation of incretin such as GLP-1 by breaking down the two terminal amino acids peptides to a shortened form, which makes the half-life shorter (less than 2 min) [32].

Dipeptidyl Peptidase -4 Inhibitors are potential candidates for the treatment of type 2 Diabetes as they prevent the rapid degradation of GLP-1 and related incretins, thereby increasing the half-life by two to three times. They increase insulin secretion and decrease glucagon secretion [33]. In the development of DPP-4 inhibitors, it is important to have high specificity to DPP-4, because DPP-8 or DPP-9 also degrades peptide hormones [34]. Berberine, an alkaloid inhibits the DPP-4, which explains the mechanism of action of its antihyperglycemic activity [35]. Some of the DPP-4 inhibitors used as antidiabetic drugs are sitagliptin [34], Teneligliptin [36], Vildagliptin [37], and Linagliptin [38].

3. G-Protein Coupled Receptor 119 (GPR 119): The G-Protein Coupled Receptor GPR 119 exhibits dull modes of action upon ligand-dependent activation on Insulin and incretin secretion in the intestine. Hence, GPR 119 is emerging as a promising tool for the treatment of type 2 diabetes mellitus without causing hypoglycemia [39]. GPR 119 agonists stimulate insulin release in glucose depended manner and induce GLP-1and glucose-dependent insulinotropic peptide secretion in enteroendocrine derived cell lines. GPR 119 agonists are also used for the treatment of obesity, which is closely related to Diabetes [40].

4. GPR 40 and GPR 120: The GPR 40 and GPR 120 are fatty acid receptors, have been proposed as a potential target for type 2 Diabetes. GPR 40, also known as Free fatty acid receptor 1 (FFAR1) is a class of G protein-coupled receptors encoded by FFAR1 gene in humans. It improves glycemic control by potentiating insulin secretion in response to medium and long-chain fatty acids [41, 42]. FFA1 is found in the highest concentration in Islets of Langerhans, activation of FFA1 results in an increase in cytosolic Ca^{2+} *via* phosphoinositidine pathway; the subsequent reaction causes the secretion of insulin. The particle PBI-4050, which is an agonist of GPR40, is under scrutiny, it stays a promising medication focusing on numerous sort of fibrosis entering stage 3 clinical preliminaries [43]. Fasiglifam (TAK-875) is a G protein-coupled receptor 40 agonists that were being researched for the treatment of type 2 diabetes mellitus (T2DM). An improvement program was ended late in stage III clinical preliminaries because of liver wellbeing concerns [44, 45].

FFAR4 is otherwise called G-protein coupled receptor 120 (GPR120). GPR120 agonist corresponds with counteraction of the event and improvement of metabolic issue, like obesity and diabetes. GPR120 actuation legitimately or by implication represses inflammation, adjusts hormone discharge from the gastrointestinal tract and pancreas, and manages lipid and additionally glucose digestion in fat, liver, and muscle tissues, which may help forestall diabetes and obesity[46]. TUG-891 is a potent and selective agonist for the long-chain free fatty acid (LCFA) receptor 4, exhibited good antidiabetic activity [47]. The antidiabetic and antiobesity activity can be improved by a combination of GPR 40 and GPR 120 agonists as it exhibits synergistic effect [48].

5. Sodium/Glucose co-Transporter 2 (SGLT2): A human protein (SGLT2) is encoded by a gene (solute carrier family 5 (sodium/glucose cotransporter) [49]. SGLT2 is responsible for the movement of glucose, amino acids, vitamins, ions, and osmolyte across the intestinal epithelium and the brush border membrane of proximal renal. The 90 % of kidney reabsorption the responsibility of SGLT2 **Fig. 1,** and hence it has got a great focus interest in the field of diabetes treatment.

SGLT2 prompts the decline in blood glucose because of the expansion in renal glucose discharge. The component of activity of this new class of medications additionally offers further glucose control by permitting expanded insulin sensitivity and take-up of glucose in the muscle cells diminished gluconeogenesis, and improves insulin discharge from the beta cells in the first stage.

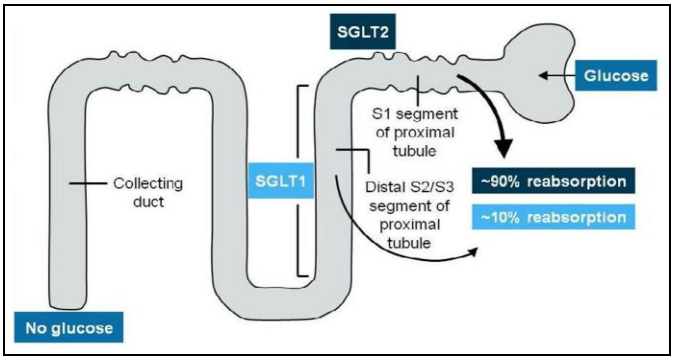

FIG. 1: MECHANISM OF ACTION OF SGLT-2

Gliflozins are also called SGLT2 inhibitors, lead to a decrease in blood glucose levels. In this way,

SGLT2 inhibitors have potential use in the treatment of type 2 diabetes. Gliflozins upgrade glycemic control just as decrease body weight and systolic and diastolic pulse. Gliflozins are an acceptable alternative for patients in which the metformin monotherapy isn't successful. They are used in combination with metformin and sulfonylureas. Dapagliflozin is an SGLT-2 inhibitor; it is a competitive, highly selective inhibitor of SGLT. It acts by means of inhibition of SGLT-2 via selective and potent action depends on every patient's fundamental glucose control and kidney function. The outcomes are diminished kidney reabsorption of glucose, glucosuria impact increments with a more elevated level of glucose in the blood dissemination. Thus, dapagliflozin lessens the blood glucose level with a component that is autonomous of insulin secretion and affectability, in contrast to numerous other antidiabetic drugs. Functional pancreatic β-cells are not necessary for the activity of the medication, so it is convenient for patients with diminished β-cell function [50]. Canagliflozin is another drug useful for type 2 diabetes and stage 3 nephropathy [51].

6. Diacylglycerol Acyl Transferase (DAGT-1): Diacylglycerol is a major type of lipid and an essential form of energy storage. However, excessive accumulation of this type of lipids in the body leads to several metabolic disorders such as obesity, hyperlipidemia, hypertension, hepatic steatosis, and insulin resistance. Diacylglycerol acyltransferases 1(DGAT 1) catalyze the final step in triglyceride biosynthesis. Therefore, inhibiting the excessive biosynthesis and storage of these lipids would be a promising therapeutic strategy for the treatment of type 2 Diabetes Mellitus [52]. The insulin sensitization and weight reduction ability of DGAT 1 has been proved in mice model using selective DGAT 1 inhibitor AZD7687 [53].

7. 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1): The cortisone reductase 11β-Hydroxysteroid dehydrogenase type 1, is an NADPH subordinate compound communicated in the liver, adipose tissue, and central nervous system. It converts the cortisol, a stress hormone into its inactive metabolite cortisone, and also catalyzes the reverse reaction, *i.e.*, conversion of cortisone to cortisol [54]. Accumulation of cortisol can lead to obesity and insulin resistance. 11β-HSD1 inhibitors restrain NADPH intervened decrease of cortisone to cortisol in tissues and improve glucose homeostasis.

In a study, Salicyaltes down-regulates the 11β-HSD1 expression in adipose tissue in obese mice, which explains why aspirin improves glycemic control in type 2 diabetes [55]. Epigallocatechin gallate, a polyphenolic constituent of green tea [56], carbenoxolone [57,] and curcumin [58] are found to be potent inhibitors of 11β-HSD1.

8. Peroxisome Proliferator-Activated Receptors (PPAR): These are a group of three nuclear receptor isoforms, PPARγ, PPARα, and PPARδ encoded by different genes. Function as transcription factors regulating the expression of genes and play an essential role in differentiation, development, and metabolism, and tumorigenesis. They play a key role in regulating lipid metabolism by acting as lipid sensors. Activation of PPARγ causes insulin sensitization and enhances glucose metabolism, whereas, PPARα and PPARδ enhances fatty acid metabolism [59]. Potent synthetic ligands such as fibrates and thiazolidinedione's are found to be effective in Diabetes [60]. Therefore, PPARγ agonists have emerged as potent insulin sensitizers used in type 2 Diabetes [61].

9. Glutamine fructoese-6-phosphate amido-transferase (GFAT): It is an enzyme in humans exists in three isoforms, GFAT1, GFAT2 and GFAT1L, among this GFAT1 is important because of its high expression in liver and fatty tissues. GFAT is involved in glucose-induced insulin resistance by its action on hexosamine biosynthetic pathway (HBP) and induces synthesis of growth factor [62]. Majority of glucose is utilized by glycolysis, only a small portion of glucose enters the hexamine pathway where fructose-6-phosphate is converted into glucosamine 6-phosphate by GFAT. The major reaction product is Uridine diphosphate N-Acetyl Glucosamine (UDP-Glc-Nac). HBP functions as important cellular nutrient and plays a role in the development of insulin resistance and vascular complications of diabetes [63].

CONCLUSION: Diabetes Mellitus is one of the most common metabolic disorders affecting larger population of the world. The frequency of diabetes is increasing because of a sedentary lifestyle,

nutritional transition, rapid urbanization; the epidemic has developed in analogs with the global rise in obesity [64]. Several antidiabetic drugs have been developed with the intention to maintain a normal blood glucose level. Diabetic patients need insulin every day because the insulin produced by the pancreas is insufficient or it is unable to reach the tissues. Several oral hypoglycemic drugs developed showed good effect but they have their own disadvantages like safety margins, adverse reactions and cost. Therefore, the research has been focused to develop drugs which act on some targets which regulate the insulin secretion and action. The important targets are as explained above. Further research on this regard would be appreciated to develop specific drugs for diabetes associated with microvascular complications.

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