Therapeutic Advances in the Management of Type II Diabetes

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Abstract

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by persistent hyperglycemia. This condition occurs due to two main factors: β-cell dysfunction and reduced response to insulin by cells and tissues with insulin receptors (insulin resistance). Insulin resistance occurs when the body fails to respond to insulin; therefore, cells and tissues are impaired in transporting glucose, leading to abnormally high glucose levels in circulation. Insulin resistance is a multifactorial condition; thus, the eminent cause is not fully known. Individual health conditions and genetic predisposition have been postulated to cause it. Molecularly, insulin resistance has been associated with complications in the glucose-fatty acid (Randle's cycle) and the activation of specific transcription factors such as FOXO1. There is no cure for T2DM, but a combination of both pharmacological and non-pharmacological therapies has been effective in managing the progression of the disease. Oral hypoglycemic agents, for instance, promote insulin sensitivity, facilitating glucose uptake. These include thiazolidinediones, sulfonylureas, and biguanides. Other agents such as dipeptidyl peptidase 4 (DPP-4) inhibitors, α-Glucosidase inhibitors, sodium-glucose co-transporter two, and glucagon-like peptide-1 receptor analog have been used in T2DM treatment. Other potential treatment options include stem cell therapy, direct lineage programming, bromocriptine, statin therapy, and inceptor receptors. Non-pharmacological approaches incorporate lifestyle changes like diet, physical exercise, and emotional treatment to manage the disease. An overview of these therapeutic strategies reveals the progress in the research aimed at finding a feasible cure for T2DM.

Type 2 Diabetes: Therapeutic Methods for Management

Type 2 diabetes is one of the most common metabolic disorders. The World Health Organization (WHO) estimates that over 90% of diabetes cases are T2DM (Galicia-Garcia et al., 2020). The statistics and data associated with the progression of T2DM are alarming. The International Diabetes Federation (IDF) recorded 4.2 million deaths and 469 million adults between 20 and 79 living with T2DM. This number is projected to rise to 700 million cases of diabetes by 2045. Aside from the implication for patients, T2DM is responsible for 720 billion USD in health expenditures, according to the data recorded in 2019. Additional studies indicate that developing countries in Africa, Asia, and South America have the highest disease cases (Koliaki & Doupis, 2011; Stumvoll et al., 2005). T2DM is caused by an interplay between two main factors: β-cell dysfunction, which leads to reduced insulin secretion, and the inability of insulin-sensitive cells and tissues to respond to insulin (Galicia-Garcia et al., 2020).

Under normal metabolic conditions, insulin controls glucose homeostasis by facilitating glucose transport and metabolism; therefore, the process accompanying insulin release and the subsequent interaction between insulin and cells and tissues with insulin receptors are closely monitored by highly coordinated intracellular processes in the body (Kahn, 2003). Insulin is a polypeptide hormone consisting of two peptide chains connected by disulfide bonds. It is synthesized as a precursor (proinsulin), which undergoes proteolytic cleavage to form insulin and C-peptides. Insulin is stored and awaits secretion by the beta cells of the pancreas. There are additional molecules in the body that trigger insulin secretion. These include incretins, hormones, nucleotides, ions, and reactive oxygen species (ROS), all of which are released during different metabolic processes (Keane & Newsholme, 2014).

The pancreas is an exocrine and endocrine organ that plays a crucial role in digestion, distinctly utilizing energy molecules. The pancreatic islet consists of three prominent cells. The alpha (A) cells that secrete glucagon, the Delta (D) cells responsible for somatostatin production, and the beta (B) cells, which are the most abundant of the cell types, facilitate insulin release (Leung, 2010). Glucose metabolism in beta cells through glycolysis leads to the formation of energy molecules NADH and $FADH_2$ through the Citric acid cycle. These molecules enter the electron transport chain in the mitochondria, where they undergo oxidation to form Adenosine triphosphate (ATP), the body's primary energy source. The formation of a high-energy environment promotes membrane depolarization, which causes the opening of the voltage-gated calcium channels. Calcium is a second messenger molecule whose influx into the secretory vesicles activates the process of exocytosis of insulin (Keane & Newsholme, 2014). Once secreted, insulin is transported to tissues and cells with insulin receptors through the hepatic portal system, where they exert their action.

Initially, insulin is produced as an inactive precursor form called preproinsulin. Preproinsulin is transported to the rough endoplasmic reticulum (RER), where it undergoes a series of cleavage processes to remove the signal peptide at the N-terminus, generating proinsulin. Proinsulin undergoes a series of folding steps in the Golgi apparatus, where the peptide bonds and disulfide bridges that connect the two insulin chains are hydrolyzed by carboxypeptidase E peptide to form active insulin that is packaged in the Golgi apparatus and stored in vesicles. The mature insulin is now ready to exert its metabolic functions and awaits signals for release (Tokarz et al., 2018). A mature insulin molecule has two peptide chains (A and B) linked together by disulfide bonds (Yu et al., 2005).

Insulin secretion can be affected by transmembrane glucose transport, certain amino acids, and certain hormones. Secretion is primarily triggered by increased glucose levels in circulation, taken up by the different glucose transporters to the beta cells of the pancreas. At this location, glucose is phosphorylated by glucokinase, which marks the initial step of assembly of the insulin secretion apparatus (Richard & Michael, 1999). Glucose metabolism enters the Krebs cycle and forms ATP. A high ATP/ADP ratio induces APT-dependent potassium channels in the plasma membrane, resulting in depolarization (Bonora et al., 2012). The depolarization receptor potential activates the opening of calcium channels, thus allowing calcium to enter the cell. Calcium acts as a second messenger that facilitates many body functions. In the insulin signaling pathway, high intracellular calcium levels prime and promote the fusion of secretory vesicles to the plasma membrane (Endo, 2006). The hypothalamus senses changes in physiological glucose levels and facilitates glucose transport to the pancreatic beta cells through glucose transporter 2 (GLUT-2) channels. High glucose concentration in the beta cells causes a depolarization event that opens the calcium channels, which facilitates calcium influx (Bonora et al., 2012).

High calcium level leads to insulin release. Insulin circulation in the blood initiates the insulin signaling cascade. Glucose homeostasis is maintained in the body during a fasted state through hepatic glucose production (HGP). This process involves catalysis of glycogen to yield glucose (Rizza, 2010). During the fed state after a meal, the beta cells produce insulin, which inhibits catabolic processes and promotes the progression of anabolic processes to facilitate glucose uptake in skeletal muscles and adipose tissue and the subsequent formation of glycogen (Moore et al., 1991). Insulin release additionally inhibits HGP and glucagon secretion from the pancreatic alpha cells. Insulin secretion is tightly regulated by insulin receptor tyrosine Kinase (IRTK). Insulin binding to IRTK causes a conformational change and autophosphorylation of the

IRTK molecule, which activates downstream binding proteins (Youngren, 2007). Insulin response to glucose increase is facilitated by the activation of phosphatidylinositol-3-OH kinase (PI3K), which potentiates the production of phosphatidylinositol-3,4,5-triphosphate (PIP3) from Phospahtidylinositol-4,5-diphosphate (PIP2). PIP3 then stimulates the phosphorylation of protein kinase B, also known as Akt, which is involved in regulating the metabolic functions of tissues involved in glucose uptake (Khalid et al., 2021).

In the skeletal muscle tissue, insulin secretion promotes glucose uptake and storage as glycogen. Insulin uptake is facilitated by glucose transporter 4 (GLUT4) concentrated in the membrane of skeletal muscles (Kadowaki et al., 2006; Leto & Saltiel, 2012). Akt causes the translocation of glucose transporter 4 (GLUT-4) to the plasma membrane of skeletal muscles through exocytosis. The presence of GLUT-4 on the membrane surfaces of tissues facilitates glucose uptake from the blood into cells and tissues that have receptors for insulin, thus causing the glucose levels in the blood to drop back to normal (normoglycemia) (Chang et al., 2004).

Insulin also promotes glycogenesis by inhibiting glycogenolysis, thus facilitating glucose homeostasis. In the liver, IRTK phosphorylates and activates insulin receptor substrates 1 and 2 (IRS 1 and IRS 2), which activate Akt 2 (Dong et al., 2008). Akt 2 inhibition of HGP upregulates glycogenesis and lipolysis. In the liver, inhibition of gluconeogenesis is facilitated by the Akt phosphorylation of forkhead box protein O1 (FOXO1), which downregulates the expression of gluconeogenic genes (Tzivion et al., 2011).

Pathophysiology of Diabetes Mellitus

Diabetes is not a single disease; instead, it is a heterogeneous group of syndromes characterized by elevated blood glucose, which can be attributed to relative or absolute deficiency of insulin (Richard & Michael, 1999). The pathophysiology of Diabetes Mellitus

involves a defect in the feedback loop between insulin secretion due to dysfunctional β-cells and impaired glucose uptake from the blood, resulting in abnormally high blood glucose levels (Cerf, 2013; Galicia-Garcia et al., 2020). The low secretory capacity of the cells indicates decreased pancreatic beta-cell function. The reduced beta-cell action can be explained through different biochemical models, such as reduced beta-cell number and exhaustion due to oxidative stress and differentiation of the cells to other cell types, which may affect their overall function (Wysham & Shubrook, 2020).

Beta Cell Dysfunction

Beta cells' effectiveness in regulating glucose homeostasis depends on overall beta cell integrity. Beta cell size, which is closely monitored during the cell cycle, has been shown to have implications on the beta cell mass, thus influencing its role in insulin secretion. A decrease of ≤ 60% in beta cell mass in T2DM patients is associated with a substantial reduction in glucose-dependent insulin secretion (Silvia et al., 2005). Beta cells regulate the insulin gene transcription, preproinsulin secretion, proinsulin biosynthesis, and eventual insulin release (Tokarz et al., 2018). Beta cell dysfunction has traditionally been linked with beta cell death. Recent research, however, has revealed more complex yet coordinated mechanisms coupled with environmental factors that play a role in causing impaired beta cell function. Beta cell dysfunction can also occur when there is an impairment in the initial process of insulin secretion, where glucose transport through the membranes and its interaction with glucose sensors to trigger insulin release occurs (Sebastian et al., 2023). Disruption of glucose transport leads to glucotoxicity, which hinders subsequent stages of insulin secretion (McClain, 2004).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed during beta cell dysfunction. Increased ROS production from the mitochondria and excessive release of

RNS from nitric oxide hinder the electron transport chain, an essential process in creating the high-energy environment that triggers insulin release (Drews et al., 2010; Jisun et al., 2012). Pancreatic beta cell dysfunction can also be caused by autoimmune destruction, which contributes to impaired insulin secretion (Richard & Michael, 1999). Insulin secretion by the pancreatic beta cell requires beta cell integrity. In pathological conditions, islet organization and efficiency can be impaired, negatively affecting cell-cell communication, contributing to poor insulin control, and, ultimately, the inability to ensure euglycemia (Kouidhi, 2012). Defects in the synthesis of intermediate precursors in the insulin secretion pathway or even insulin itself indicate failed beta cell function and lay the foundation for the development of T2DM. Reduced beta-cell mass leads to low insulin secretion. Insufficient insulin secretion by pancreatic beta cells causes insulin resistance (Richard, 1999).

Insulin Resistance

Insulin resistance is a state of reduced responsiveness to physiological insulin levels by the insulin-targeting cells, primarily the liver, muscles, and adipose tissue, or at a systemic level, an impaired response to circulating insulin by blood glucose levels. There are three broad categories of insulin resistance: diminished insulin secretion by beta cells, insulin antagonists that impair insulin signaling in the plasma, and impaired insulin response in target tissues (Pearson et al., 2016). The skeletal muscle is a significant site for insulin-stimulated muscle glucose uptake, which is facilitated by GLUT4 translocation. Insulin resistance in the skeletal muscles is majorly attributed to defects in the GLUT4 translocation to the membrane, such as mutations that downregulate the expression of the transporter. Insulin resistance can also be caused by defects in the insulin secretion cascade, which directly inhibits downstream events (Le Marchand-Brustelet al., 1985).

Insulin resistance in the liver is marked by the inability to regulate HGP, which causes hyperglycemia. Lack of control in regulating gluconeogenesis and the de-suppression of FOXO1 provides insight into the development of insulin resistance in the liver and adipose tissue (Magnusson et al. 1992). The adipose tissue is additionally affected by insulin resistance. Adipocytes are very metallically active cells and can synthesize compounds that directly regulate glucose homeostasis. These compounds can hinder the function of Akt, thus leading to GLUT4 impairment and facilitating insulin resistance (Capurso & Capurso, 2012). The mechanism of insulin resistance has not been fully established. However, theories exist that provide an understanding of what happens during insulin resistance.

One mechanism to explain insulin resistance is the glucose-fatty acid cycle (the Randle cycle) (Lee et al., 2022). During this metabolic process, there is an increase in fatty acid oxidation, which hinders insulin-stimulated glucose metabolism and utilization through the inhibition of downstream enzymes that facilitate glycolysis. Fatty acid oxidation upregulates acetyl-CoA production, a substrate that inactivates pyruvate dehydrogenase, leading to increased citrate levels. As a result, glucose and fatty acids compete for activation and uptake into muscles and adipose tissue (Randle et al., 1963). High citrate level in the cytosol inhibits phosphofructokinase 1 (PFK1), a key regulatory enzyme in glycolysis. This causes the accumulation of glucose 6-phosphate that eventually inhibits hexokinase 2. A dysfunctional hexokinase 2 hinders glucose uptake through glucose transporter 4 (GLUT 4), an essential carrier in skeletal muscle cells and adipocytes. This leads to increased glucose levels in circulation, resulting in hyperglycemia. Impaired glucose transport can also be due to complications in the tyrosine kinase pathway that facilitates glucose transport (Lee et al., 2022).

In the liver, insulin resistance is triggered by insulin-induced glycogen synthesis. The de-suppression of a transcription factor FOXO1 in the liver has been shown to induce insulin resistance. FOXO1 is a transcription factor actively regulating gluconeogenesis and glycogenolysis by controlling insulin signaling by recognizing insulin response elements (IRE), which are vital in maintaining glucose levels. Under normal conditions, FOXO1 is suppressed through phosphorylation events, leading to a decreased glucose release rate; hence, the body's glucose levels remain within the normal range. The de-suppression of FOXO1, however, upregulates glucose release by gluconeogenesis, thus increasing glucose levels above average and resulting in hyperglycemia, which, if left untreated, results in the endoplasmic reticulum (ER) stress and, eventually, insulin resistance (Lee et al., 2022). Insulin resistance additionally affects the liver's section by blocking glycogen synthesis, enhancing lipolysis, and facilitating the production of pro-inflammatory proteins that further lead to oxidative stress, exacerbating the progression of insulin resistance (Leclercq et al., 2007).

Insulin resistance can also be explained using the hexosamine biosynthesis pathway. During this process, fructose-6-phosphate is produced by glucose-6-phosphate during glycolysis, which is metabolized to fructose-1,6-bisphosphate. Some fructose-6-phosphate is converted to glucosamine-6-phosphate by glutamine (Marshall et al., 1991). Glucosamine-6-phosphate is converted to uridine 5'-diphosphate N-acetylglucosamine (UDP-GlcNAc), which participates in the glycosylation of proteins and lipids. Regulation of enzymatic properties and modifications to proteins could affect transcription, thus affecting their functions (Hawkins et al., 1997). O-GlcNAcylation has been postulated to compete for phosphorylation on the active site, which could affect the functions of IRS-1/2, Akt, and other regulatory molecules involved in propagating the insulin signaling cascade. Defects in the insulin signaling cascade additionally

affect the movement of GLUT4 to the membrane surface, thereby reducing the glucose uptake rate (Ball et al., 2006).

Fatty acid formation through lipolysis is also linked to the pathogenesis of insulin resistance. This metabolic process facilitates the accumulation of lipid intermediates such as lysophosphatidic acid (LPA), diacylglycerols (DAGs), and triacylglycerol. These compounds may assume secondary roles and act as second messengers in the progression of insulin resistance (Samuel et al. 2012). In lipid-induced insulin resistance, any defect in the insulin signaling cascade leads to the activation of novel protein kinase C (nPKC), increasing the DAG level in the blood (Karasik et al., 1990). A high cytosolic DAG level in the liver activates nPKC. It facilitates translocation to the membrane, inhibiting IRTK and preventing the activation of essential molecules, thus disrupting the propagation of insulin signals and enhancing the etiology of insulin resistance (Samuel et al., 2012).

Chronic inflammation additionally promotes the development of insulin resistance due to the production of cytokines and pro-inflammatory signals such as tumor necrosis factor-α (TNFα), interleukin-6 (IL-6) and interleukin-8 (IL-8) (De Luca & Olefsky, 2008). Inflamed adipocytes trigger the movement of macrophages to the neighboring cells, releasing cytokines that augment the inflammatory response, thus leading to insulin resistance. TNFα expression, for instance, leads to the activation of NFkBa transcription factor that encodes several inflammatory mediators, hence promoting the pathogenesis of insulin resistance (Yekollu et al., 2011).

Enteral and Parenteral Hypoglycemics

An interaction between genetic, environmental, and lifestyle factors causes diabetes. The combination of these factors and how they relate to each other in promoting the progression of Type 2 diabetes mellitus (T2DM) has helped provide additional insight into ongoing efforts to

develop a more permanent therapeutic approach to treat and manage the disease. Pharmaceutical approaches in oral and injectable medication have been practical in managing T2DM, which could be either monotherapy or combinational therapy, where multiple drugs address multiple symptoms simultaneously.

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin sensitizers and include drugs such as pioglitazone and rosiglitazone (Richard & Michael, 1999). These drugs lower insulin resistance, reduce fatty acid synthesis, and increase insulin sensitivity. TZDs have a high affinity binding to the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ), a transcription factor expressed mainly in the white adipose tissue (Tontonoz et al., 1994). PPARγ forms a dimer with retinoid X receptor (RXR) in the cells. The PPARγ-RXR complex proceeds to bind PPARγ response elements in target genes, thus regulating transcription of insulin-responsive genes (Reginato & Lazar, 1999). The activation of PPARγ promotes the transcription of several insulin-reactive genes involved in regulating glucose levels in the blood by controlling glucose metabolism. This increases insulin sensitivity in the adipose, liver, and skeletal muscles. Rosiglitazone, a type of thiazolidinedione, has a greater binding affinity for PPARγ thus effective in reducing glycemia in T2DM patients (Harold et al., 2001). TZDs promote fat metabolism and distribution in the adipose tissue (Richard & Michael, 1999; Tsoutsouki et al., 2020). TZDs additionally affect cytosolic cholesterol levels. Rosiglitazone, for instance, increases low-density lipids (LDL) cholesterol, while pioglitazone decreases triglycerides, which is more effective in obese diabetic patients (Richard & Michael, 1999).

Insulin resistance is caused by the expression of TNFα, which upregulates the production of inflammatory cytokines. TZDs, however, counter this by promoting insulin sensitivity. TZDs additionally promote the phosphorylation and activation of molecules involved in the insulin signaling cascade, which would otherwise be inhibited by the expression of TNFα (Katsuki et al., 2000). Thiazolidinediones additionally downregulate the secretion of pro-inflammatory cytokines tumor necrosis factor α (TNFα) and interleukin six that are involved in causing insulin resistance while upregulating levels of adiponectin that functions to sensitize cells and tissues to insulin and reduces inflammation. The combined effect of adiponectin increases insulin secretion (Stumvoll et al., 2005). Thiazolidinedione, however, has been associated with weight gain due to the ability of the drug to promote TAG storage, thus increasing total body fat. TZDs also promote increased plasma volume and fluid retention, which might cause pulmonary edema (Schoonjans & Auwerx, 2000).

Sulfonylureas

Sulfonylureas are a group of drugs that promote insulin release from beta cells independent of blood glucose levels and require the presence of functional beta cells (Sola et al., 2015). The drugs can be divided into two generations, with gliclazide, glipizide, glibenclamide, and glimepiride being in the second generation and widely used. At the same time, tolbutamide and chlorpropamide are the first generation and are no longer used. These drugs bind and block the ATP-sensitive potassium channel's subunit, reducing potassium efflux (Philipson & Steiner, 1995). This causes calcium channels to open and the subsequent calcium entry. High intracellular calcium levels and membrane depolarization stimulate insulin release from the pancreatic beta cells (Mahler &Alder, 1999; Richard & Michael, 1999). The drugs additionally

reduce hepatic glucose release and increase peripheral insulin sensitivity. Sulfonylureas can, however, lead to weight gain and hypoglycemia among patients; hence, it should be used with caution to avoid excessive accumulation in the body (Mahler &Alder, 1999).

Biguanides

Biguanides include metformin and are categorized as insulin sensitizers. Metformin's inotropic property allows it to work on multiple tissues (Mahler &Alder, 1999). This facilitates increased insulin uptake and use by the target tissues, thus reducing the likelihood of insulin resistance. The drug also reduces hepatic gluconeogenesis, slows down intestinal absorption of sugar, and upregulates peripheral glucose uptake and utilization. Another joint oral agent used alongside biguanides to manage T2DM is glinides. These drugs, such as repaglinide and nateglinide, stimulate the beta cells to release more insulin (Philipson & Steiner, 1995). Like sulfonylureas and biguanides, glinides act by binding specific sites of beta cells. This event inhibits ATP-sensitive K channels and initiates depolarization and downstream events that cause insulin secretion (Richard & Michael, 1999).

Meglitinides

Meglitinides are a class of oral medications that stimulate beta-pancreatic cells to produce insulin. They include: repaglinides and nateglinides (Black et al., 2007). The mechanism of action of these drugs involves binding ATP-dependent potassium channels, leading to their eventual closure (Sunaga et al., 2001). Closed potassium channels initiate a depolarizing event that opens calcium channels and the subsequent exocytosis of insulin. Meglitinides have, however, been shown to cause hypoglycemia and, eventually, weight gain in patients (Tran et al., 2015).

α-Glucosidases Inhibitors

α-Glucosidase inhibitors include drugs such as acarbose and miglitol. α-glucosidases are brush border enzymes found in the small intestines that facilitate the breakdown of carbohydrates to glucose and other simple sugars for absorption (Chiba, 1997). The glucosidases are additionally involved in other intracellular processes, such as lysosomal glycoconjugate catabolism and post-translational modifications (Kashtoh & Baek, 2022). When taken before a meal, α-Glucosidase inhibitors prevent the enzymatic activity, thus less carbohydrate breakdown. This reduces glucose absorption in the small intestines, lowering postprandial glucose levels (Derosa & Maffioli, 2012). An added benefit of using acarbose is its role in resulting in weight loss among patients, but the mechanism by which this occurs is still unclear.

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors, also called gliptins, are a class of hypoglycemic drugs also used in patients with T2DM (Knudsen & Pridal, 1996). They include alogliptin, linagliptin, saxagliptin, and sitagliptin. DPP-4 is a ubiquitous enzyme found in the endothelium of different organs in the body (Gilbert & Pratley, 2020). The enzyme cleaves and inactivates GLP-1 and readily degrades other peptides and amino acids in the body. The drugs interact with incretin hormones, specifically glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), that are released shortly after a meal, thus augmenting insulin secretion, reducing glucagon release, and delaying gastric emptying, lowering blood glucose levels. (Drucker & Nauck, 2006). Under normal physiological conditions, the DPP-4 enzyme degrades the incretin hormones shortly after secretion. The DPP-4 inhibitors, however, hinder the catalytic functions of the enzyme, a process that ensures high GLP-1 and GIP levels in circulation and the

eventual insulin secretion by pancreatic beta cells and reduced glucagon secretion (Burcelin et al., 2001). The weight-neutral property of DPP-4) inhibitors makes them a common target in weight loss programs (Foley & Jordan, 2010). Gliptins, however, are associated with significant risk factors for heart attack, stroke, coronary disease, and upper respiratory tract infections (Seshadri & Kirubha, 2009).

Sodium-glucose Co-transporter 2 Inhibitor

Sodium-glucose co-transporter 2 (SGLT) inhibitors include canagliflozin and dapagliflozin. SGLTs are a group of proteins primarily found in the kidney that play a crucial role in ensuring glucose homeostasis in the body (Kalra, 2014). This protein has two isoforms, SGLT-1 and SGLT-2, which vary depending on their locations and their involvement in glucose transport (Chao, 2014). SGLT-2 is the primary transporter responsible for most of the glucose reabsorbed in the kidney nephron. The oral agents, SGLT-2 inhibitors, block glucose uptake from the glomerular filtrate, thus lowering glucose circulating in the blood and increasing glucose excreted in urine (List et al., 2009). Clinical trials show that (SGLT) inhibitor treatment causes weight loss in patients. (Janež & Fioretto, 2021) The weight reduction rate is slow, and the mechanisms involved are complex.

Glucagon-like Peptide-1 Receptor Analogs

Glucagon-like peptide receptor analogs (GLP-1 RA) regulate glucose homeostasis by inhibiting glucagon release from the pancreatic α-cells (Tsoutsouki et al., 2020). Glucagon-like peptide-1 (GLP-1) is a pluripotent incretin hormone secreted in response to ingestion of food. GLP-1 action is mediated by GLP-1 receptors, which are found in multiple body parts, including the heart, kidney, pancreatic islets, lungs, and the gastrointestinal tract. Under normal physiological conditions, (GLP-1) prolongs food movement from the stomach to the intestines;

thus, the food takes longer to be absorbed, promoting satiety. This phenomenon is known as the incretin effect. The use of GLP-1 receptor analogs stimulates the pancreatic beta cells to secrete insulin using the enzyme adenyl cyclase.

GLP-1 also facilitates insulin synthesis from proinsulin and inhibits glucagon release. The combined effects of GLP-1 RA (increased insulin release and reduced glucagon secretion) protect patients from hyperglycemia (Koliaki & Doupi, 2011). GLP-1 also raises cyclic AMP levels in adipocytes, activating AMPK in the liver. AMPK facilitates the transcription of the SREBP-1c gene that regulates the transcription of other genes in the lipolysis pathway. The inhibition of lipolytic genes leads to reduced lipid oxidation (Erion et al., 2016). These drugs have been linked with weight loss in obese patients. GLP-1 suppresses appetite, thus reducing the frequency of ingestion (Vilsbøll et al., 2012).

Other Potential Treatment Options

Stem Cell Therapy

Stem cell therapy as a therapeutic method for the treatment of T2DM has shown promise as it provides solutions to some of the problems associated with traditional diabetic treatment methods. Exogenous insulin administration, for instance, involves daily injections, often associated with complications such as hyperglycemia due to defects in glucose metabolism (Tiwari, 2015). One of the significant causes of T2DM is beta-cell dysfunction. Stem cell therapy involves the removal of dysfunctional pancreatic β-cells and replacing them with healthy islets, thus ensuring the production, storage, and supply of insulin (Farooq et al., 2018). Current research focuses on pancreatic and beta cell transplants using embryonic stem (ES) cells. ES cells are pluripotent, meaning they can differentiate into various adult cell types. When subjected to the right conditions and signals, ES cells can give rise to viable pancreatic islet cells, which

can be substituted for dysfunctional ones. A successful transplant leads to glycemic control; thus, stem cell therapy remains the most promising therapy and potential permanent cure for T2DM (Rahim et al., 2018). Stem cell therapy, however, is accompanied by complications such as infectious diseases (Khamaisi & Balanson, 2017).

Additional limitations on adopting stem cell therapy in clinical settings are the shortage of embryonic stem cells, ethical regulation, and the possibility of cell rejection by the recipient (Meier et al., 2006). Continued research in stem cell technology has shown progress in using mesenchymal stem cells (MSCs) from adult tissue (Si et al., 2012). MSCs enhance the regeneration of pancreatic beta cells and offer protection from apoptosis, thus reducing the progression of insulin resistance in different tissues (Gao et al., 2014). Like ESCs, bone marrow-derived MSCs (BM-MSCs) can transform into insulin-producing cells (IPCs). BM-EMCs also participate in the repair process of restoring the damaged pancreatic beta-cells by facilitating the production of different growth factors (Caplan & Dennis, 2006).

Direct Lineage Programming

Another approach that has shown promise as an area of study in managing diabetes mellitus is direct lineage reprogramming. Cellular reprogramming is a fast-growing facet of regenerative medicine (Li et al., 2014). Direct lineage reprogramming involves the conversion of one differentiated cell into a different cell without going through the pluripotent stage, in the case of T2DM, converting any cell type to pancreatic beta cells. One of the causes of beta cell dysfunction is reduced beta cell mass due to atrophy, thus causing a loss of efficiency in insulin secretion. The discovery of transcription factors Pdx1, Neurog3, and MafA has been foundational in facilitating the conversion of acinar cells into cells that secrete insulin (Zhou et al., 2008). Research shows that the Neurog3 transcription factor can suppress the expression of

some genes in acinar cells, forcing them to become beta cells (Li et al., 2014). This method has increasingly been used in the production of cell types and has demonstrated some potential to be used as a therapeutic approach. Since diabetes mellitus is caused by a lack of functional β-cells, cell replacement therapy can be incorporated to substitute the dysfunctional receptor cells. With appropriate reprogramming factors, adult cells can be induced into other cell types. The ability to convert various pluripotent cells to beta cells provides a promising alternative for managing and possibly curing T2DM (Fontcuberta-PiSunyer et al., 2023).

Bromocriptine

Diabetes mellitus can additionally be managed using oral agents. Bromocriptine is a drug used to treat T2DM, and it promotes glycemic control and glucose tolerance in obese patients (Thulé, 2012). Bromocriptine (cycloset) works by activating dopamine receptors. Recent research shows elevated serotonin, epinephrine, and norepinephrine levels and decreased dopamine levels during insulin resistance. These metabolic and neurogenic changes are similar to those observed in obese patients, characterized by a high frequency of insulin resistance (Defronzo, 2011). The use of bromocriptine in obese diabetes patients showed a significant reduction in glucose levels. Bromocriptine activates more dopamine receptors, which increases dopaminergic tone and reduces sympathetic activities. This triggers a cascade of events, including decreased hepatic glucose release, resulting in reduced glucose levels in circulation. Bromocriptine also reduces glucose intolerance in patients (Thule, 2012).

Inceptor Receptor

While different therapeutic approaches have been effective in managing type 2 diabetes, no therapy has successfully reversed or cured the disease. Recent research, however, indicates promising results through the discovery of an insulin-inhibitory receptor inceptor. Inceptor

promotes the sensitization of insulin pathways by increasing β-cells mass. This, in turn, increases β-cells function in insulin secretion and consequently reduces hyperglycemia. Inceptors have an AP2 adaptor complex in their cytoplasmic domain, which promotes clathrin-mediated endocytosis, facilitating transport (Ansarullah & Far, 2021). Since insulin resistance is characterized by the desensitization of insulin-responsive tissues and cells to insulin, it would be reasonable to think that research to reverse the process would be effective and appropriate. An inhibitor has been shown to induce the regeneration of pancreatic beta cells and the subsequent increase in the sensitivity of the cells to insulin.

Statin Therapy

Statin therapy is used as a primary and secondary method to reduce the prevalence of cardiovascular diseases. Statin is a lipid-lowering agent that inhibits the function of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), an enzyme that converts HMG CoA to mevalonic acid, the rate-limiting step in cholesterol synthesis (Buse, 2003). Recent findings have shown a high mortality rate in diabetes patients from cardiovascular disorders due to the accumulation of low-density lipids (LDL) cholesterol. Statin facilitates the expression of LDL receptors in the liver, which bind LDL and VLDL molecules, thus resulting in low cholesterol circulation in the blood (Tiwari, 2015). Statin additionally increases the amount of high-density lipid (HDL) cholesterol and triglycerides (TAGs) in circulation, thus reducing the mortality rate from heart attack (Stumvoll et al., 2005). Statin has since been adopted in treating T2DM, specifically obese patients, due to its cholesterol-reducing abilities.

Despite statin's success in lowering blood cholesterol levels, there have been speculations that statin causes insulin resistance. Statin-induced insulin resistance occurs due to the inhibition of isoprenoid synthesis and reduced C/EBPα production, thus affecting the transcription of some

prominent genes in the body (Nataka et al., 2006). Reduced isoprenoid synthesis additionally leads to reduced GLUT4 expression on fatty tissues, thus reducing glucose uptake. This potentiates reduced insulin-induced glucose uptake (Kanda et al., 2003). Another negative implication of statins is their suppression of insulin secretion due to low ATP levels due to ubiquinone synthesis inhibition (Yada et al., 1999).

Non-pharmacological methods

The pharmaceutic approach is partly practical in the long-term management of T2DM. Several lifestyle modifications and adjustments of certain environmental factors can augment the success of managing the disease. Dietary changes, physical activity, emotional therapy for stress management, and improved sleep patterns are a few of the most commonly used methods.

Dietary Changes

Dietary habits are closely linked with an individual's ability to manage various metabolic disorders. Diabetes has been described as a disorder of carbohydrate metabolism due to hyperglycemia, an indication of the disease (Sheard et al., 2004). The constituents of a person's diet determine the blood glucose level, with carbohydrates having the most influence. A high intake of other foods, such as red and processed meat and foods with high saturated fat content, is directly associated with the development of T2DM (Marion et al., 2014). One way to keep track of blood glucose levels based on the diet is using glycemic index. The glycemic index is the classification of carbohydrate foods based on their effect on plasma glucose. The values obtained after that can be used to make dietary choices (Sheard et al., 2004). The glycemic index, however, has limitations as it only provides information on how the quality of carbohydrates affects glucose levels and nothing about the implications of quantity. As a result, glycemic

control should be used in conjunction with other nutrient strategies (Ludwig & Eckel, 2002; Sheard et al., 2004).

Intake of fruits and vegetables as part of a healthy diet, for instance, contributes to reduced risk for T2DM as these foods are rich in necessary nutrients such as vitamins, antioxidants, and potassium (Wang et al., 2016). Patients with T2DM can also adopt various diets. The Mediterranean diet, for instance, involves consuming legumes, fruits, vegetables, whole grains, and nuts. More extended periods of following the diet have been linked with inducing glycemic control in T2DM patients (Marion et al., 2014). Incorporation of the Paleolithic diet plan, which emphasizes the consumption of lean meat, fish, vegetables, and fruits, additionally shows an improved ability to maintain normal glucose levels (Borse et al., 2021).

Physical Activity

Studies have shown a direct correlation between physical activity and the ability to maintain euglycemic glucose levels and reduced risk of cardiovascular disease (Hamasaki, 2016). Regular physical exercise increases myocardial blood circulation and upregulates high-density lipids (HDL) cholesterol levels, which reduces heart stress (Pinckard et al., 2019). Moderate, daily physical activity also promotes energy expenditure and thus effectively contributes to weight loss and managing T2DM (Hamasaki, 2016). Walking, for instance, allows glycemic control in patients who are already physically weak to engage in rigorous exercise. (Borse et al., 2021). There is a direct correlation between skeletal muscle GLUT 4 composition and their ability to transport glucose in response to insulin and exercise (Henriksen et al., 1990). Exercise induces the expression of GLUT 4 mRNA in human skeletal muscles, stimulating the

synthesis of GLUT 4 transporter, which functions to transport glucose, maintaining a stable glucose level (Flores-Opazo et al., 2020).

While daily physical activity can be incorporated into the everyday life of diabetic patients, caution should be taken on the intensity of the training. T2DM patients typically have weaker physical performance than their non-diabetic counterparts. Moreover, lifestyle modifications have been shown to help manage T2DM. A sedentary lifestyle in T2DM patients is linked to decreased energy expenditure, uncontrolled glucose levels, and increased propensity for insulin resistance (Borse et al., 2021).

Emotional Therapy for Stress Management

Physiological stress has been shown to promote the onset of T2DM. In the event of stress, the body responds by increasing the activity of the sympathetic nervous system, followed by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to the release of the hormone cortisol from the adrenal cortex (Rosmond & Björntorp, 2000). Cortisol affects the functions of different body systems, including the tissues involved in lipid and glucose metabolism (Baxter & Forsham, 1972).

In T2DM, glucocorticoids that would otherwise lead to decreased food intake trigger the motivation for appetitive behavior, thus resulting in overconsumption of comfort foods, typically high in carbohydrates and fats (Rabasa & Dickson, 2016). This contributes to increased blood glucose in circulation and metabolic stress that eventually causes insulin resistance (Hackett & Steptoe, 2017). Glucocorticoids are steroid hormones secreted in stressful situations and are essential in regulating blood glucose levels. In the liver, glucocorticoids facilitate gluconeogenesis, which reduces glucose utilization and uptake by the skeletal muscles (Kuo et al., 2015). Glucocorticoids additionally antagonize the role of insulin in promoting glucose

uptake; therefore, chronic stress and eventual long-term exposure to glucocorticoids may cause hyperglycemia and insulin resistance, both of which are hallmarks of T2DM (Di Dalmazi et al., 2012). Stress additionally negatively affects the responsiveness of T2DM patients to medication, making it harder to maintain the progression of the disease. Therefore, effective stress management techniques are crucial for T2DM patients as one of the strategies to manage the disease (Kelly & Ismail, 2015).

Conclusion

T2DM is a chronic metabolic disorder closely associated with severe hyperglycemia. If uncorrected, diabetes can lead to other health complications such as heart damage, kidney disease, and vascular disorders. Some risk factors linked to T2DM are genetic predisposition, epigenetics, mitochondrial degranulation, and lifestyle factors such as diet and sedentary lifestyle. The increasing prevalence of T2DM has become a problem in health care worldwide. The WHO estimates that over 90% of all diabetes cases are T2DM, and about 469 million people live with T2DM, and the number is projected to increase (Galicia-Garcia et al., 2020).

The alarming rate at which the disease is projected to grow has been influential in prompting every research effort channeled to developing new therapeutic agents to treat the disease. Some common medications include sulfonylureas, biguanide, thiazolidinediones, bromocriptine, α-glucosidase inhibitors, DPP-4 inhibitors, and GLP-R analogs. These drugs function to increase the rate of insulin production, which facilitates glucose uptake. In addition to pharmacological treatment, T2DM can be managed through lifestyle modifications such as daily exercise, dietary changes, and emotional therapies. Treatment of T2DM may involve monotherapy, where one drug is used to treat a particular symptom, or combinational therapy,

where multiple drugs are used to treat different symptoms at the same time. This augments the effectiveness of the drugs to manage the disease.

Some drugs and novel laboratory procedures that have shown potential in managing diabetes include Inceptor receptors, which have succeeded in sensitizing the insulin signaling pathway and thus could be a way to reverse insulin resistance. Inceptor receptors, however, have yet to be used in clinical settings. Direct lineage programming has also shown some promise in a lab setup promoting the regeneration of beta cells from different cell types. Stem cell technology of ES cells has also succeeded in giving rise to pancreatic cells, thus offering a way to fix beta cell dysfunction. Despite the positive results, these methods are yet to be used in a clinical setting, but this shows the progress made on the road to finding a permanent cure for T2DM.

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