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Current Therapeutic Approaches and Future Prospects for Diabetes Management: A Comprehensive Review

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Abstract. Diabetes is a common disease worldwide which prevalence has been increasing and affecting millions of lives in the world. The recently released innovations on diabetes management have delivered promising outcomes and future perspectives of studies continue to bring hopes to patients with diabetes. This review discusses the major types of diabetes and their physiology. The different treatment options as well as future therapeutic perspectives are also highlighted. Research on diabetes control is continuous, and new treatment options are being daily studied in order to improve patients' safety and quality of life even 100 years after the discovery of insulin. A deeper understanding of the physiology and pathophysiology associated with this multifactorial disease would ensure the development of safe, effective and long-lasting therapeutic options.

Keywords: diabetes, insulin, physiology, therapeutic options

Introduction

Diabetes is a disease that has become extremely common worldwide with an increased prevalence. It results in high levels of sugar in the blood over prolonged periods of time (American Diabetes Association, 2012; The Lancet, 2017). Usually, when levels of sugar increase in the body (especially after meals), insulin is released from the beta cells in the pancreas and stimulates the body cells to remove glucose from the blood allowing its absorption and metabolism into muscle, fat and liver (American Diabetes Association, 2012). In this review we will identify and describe the types of diabetes, differentiate and classify them, explore complications that may arise due to the development of diabetes, convey and communicate current treatments that may ease the symptoms and even cure diabetes.

Types of Diabetes and the Micro and Macrovascular Complications

Types of Diabetes

Type 1 Diabetes Mellitus (T1DM)

T1DM constitutes roughly 5-10% of all cases of diabetes in the world (Atkinson et al., 2014; Daneman, 2006) and recent data show an increasing prevalence among youth ranging from 179,388 in 2010 to 587,488 in 2050 (Imperatore et al., 2012). It has a strong genetic component although other factors, such as exposure to viruses and other underlying health conditions can play a role in its development (Oram et al., 2016). The occurrence of T1DM has been associated to the activation of autoantibodies that attack the insulin-producing cells of the pancreas due to the presence of autoantibody antigens on their surface. Consequently, beta cells are destroyed leading to lower insulin secretion. Thus, people who have T1DM must constantly monitor their blood glucose levels through proper measuring tools and take insulin as part of

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their treatment for all their life (McLaughlin et al., 2016; Regnell & Lernmark, 2017; Roep, 2003; N. J. Thomas et al., 2018).

Type 2 Diabetes Mellitus (T2DM)

T2DM is characterized by a progressive decline in beta-cell function and insulin resistance (Butler et al., 2003; Chatterjee et al., 2017; Defronzo, 2009; Imperatore et al., 2012). It is the most common form of all diabetes types with an incidence rate of about 90% of all cases diagnosed worldwide (Imperatore et al., 2012), and it is estimated that the number of young people with T2DM will increase from 22.820 in 2010 to 84.131 in 2050 (Kwak & Park, 2016). T2DM has a stronger link to genetics and family history than type 1 although lifestyle factors are critical for its development (Olokoba et al., 2012; Pearson, 2019; Pearson et al., 2003; Stančáková & Laakso, 2016; Weyer et al., 1999). Scientists were able to identify 75 common genetic locations/variants associated with T2DM in patients but the molecular mechanism through which those genetic variants contribute to the pathogenesis of the disease is still unknown (Weyer et al., 1999). Gene expression is influenced also by environmental factors through epigenetic changes. Indeed, deoxyribonucleic acid (DNA) methylation at cytosine and guanine separated by a phosphate (CpG) locus is a well-known epigenetic mechanism that results in lower gene expression by interacting with histone deacetylases or interfering with transcription-factor binding. Genome-wide DNA methylation analysis has shown T2DM -associated changes in DNA methylation that has the potential to be used as a promising T2DM biomarker and to develop therapeutic strategies for the disease (Weyer et al., 1999).

Other Types of Diabetes

Gestational

Gestational diabetes mellitus (GDM) is a temporary form of diabetes occurring during pregnancy due to insulin resistance and/or pancreatic dysfunction with a prevalence rate ranging between 9 to 25% of all pregnancies worldwide (Alejandro et al., 2020; Alfadhli, 2015; American Diabetes Association, 2013). During pregnancy the release of estrogen, progesterone and cortisol increases, influencing how the cells of the body respond to insulin and trigging fluctuations in the blood sugar levels. In particular, insulin resistance during pregnancy has been linked to molecules secreted by the placenta, such as tumor necrosis factor, placental lactogen, and human placental growth hormone (Coustan, 2013). In those women whose pancreas is unable to adjust to increased insulin demand hyperglycemia develops resulting in GDM. Then, diet and lifestyle changes are highly recommended together with blood glucose monitoring and pharmacotherapy including insulin injections for severe cases (HAPO Study Cooperative Research Group et al., 2008; Lende & Rijhsinghani, 2020). An early screening for GDM especially in women with risk factors is critical to avoid complications in pregnant women and their offspring (Lende & Rijhsinghani, 2020). Indeed, children of women with GDM have a high risk of developing diabetes or prediabetes at young age compared to offspring of women without diabetes making GDM a pathology responsible for the spread of diabetes in future generations (Damm, 2009; Nankervis et al., 2018).

Genetic defects of beta cell or insulin function

Genetic mutations affecting proteins responsible for regulation of insulin and beta cell functions cause diabetes (Christensen & Gannon, 2019; Donohue & Uchida, 1954; Gloyn, 2003). For instance, glucokinase (GCK) is an enzyme that regulates the amount of insulin secreted by beta cells and around 200 mutations in this gene have been associated to different diabetes phenotypes. Any functional DNA mutations in the GCK gene can potentially result in lower (hypoglycemia) or higher levels of sugar (hyperglycemia) in the blood due to increased or decreased amount of insulin released (Horikawa et al., 1997). Indeed, specific heterozygous inactivating mutations in the GCK gene have been observed and cause mild diabetes in adults, called maturity onset diabetes of the young (MODY2), while homozygous mutations in the

gene result in permanent neonatal diabetes mellitus (PNDM). A mutation in the heterotropic allosteric activator site of the enzyme causes, instead, hypoglycemia (Horikawa et al., 1997). The hepatocyte nuclear factor 1α (HFN1α) is a transcription factor controlling gene expression during embryonic development and in adult tissues and it is expressed in pancreatic beta cells. Several loss of function mutations in this gene cause beta cell dysfunction and maturity onset diabetes (MODY3) (Kadowaki et al., 1991; Kristinsson et al., 2001; Lindner et al., 1999; Magré et al., 2001). Similarly, HFN4α is a transcription factor expressed in liver, gut and pancreas and regulates the expression of genes involved in the metabolism of glucose, fatty acids and amino acids. Mutations in various domains of the transcription factor result in defective function of HFN4α and lead to diabetes (MODY1) (Rubio-Cabezas et al., 2010; Stoffel & Duncan, 1997). Inactivating mutations in the insulin promoter factor 1 (IPF1), a pancreatic beta cell specific transcription factor, leads also to agenesis of the pancreas and diabetes (MODY4) (Stoffers et al., 1998). A form of maturity onset of diabetes has been associated to mutations also in neurogenic differentiation 1 (NEUROD1), a helix-loop-helix transcription factor that regulates the expression of insulin. In particular, two mutations in the DNA binding domain and trans-activation domain that inactivate the protein cause T2DM in humans together with neurological alterations, such as learning difficulties, sensorineural deafness, visual impairment, and other symptoms (Thomas et al., 2002). Another genetic disorder, called Berardinelli-Seip Syndrome, characterized by absence of adipose tissue and severe insulin resistance includes diabetes as complication. The syndrome is an extremely rare autosomal recessive disease and is caused by mutations in the gene Berardinelli-Seip congenital lipodystrophy 2 (BSCL2), an endoplasmic reticulum protein involved in preadipocyte differentiation and lipid droplet metabolism (Wang et al., 2000).

Pancreas damage

Diabetes can occur following pancreas damage and is, then, classified as type 3c diabetes or pancreatogenic diabetes. Type 3c diabetes can be a result of several diseases, such as chronic pancreatitis, pancreatic ductal adenocarcinoma, haemochromatosis, pancreatic surgery, and cystic fibrosis (Hart et al., 2016; Kim et al., 2011; Moran et al., 2010; Pannala et al., 2008; Slezak & Andersen, 2001). In all these cases, there is a reduction of beta cell mass with consequent reduction of insulin release. In order to maintain optimal insulin levels in the blood, the remaining beta cells try to release more insulin that results in cellular stress and ultimately in cellular dysfunction. At the end, less insulin is produced resulting in a hyperglycemia and diabetes.

Hormonal-induced

Diabetes can be caused also by excessive amounts of circulating hormones (ex. growth hormone, cortisol, glucagon, epinephrine, somatostatin) (Alexopoulou et al., 2014; Han et al., 2016; Hansen et al., 1986; Khatiwada et al., 2020; Kim et al., 2005; Møller et al., 1992; Pivonello et al., 2008; Rooney et al., 1993; Song et al., 2018; Tomassetti et al., 2001). Glucagonoma is a very rare tumor of the pancreatic alpha cells that leads to large amount of glucagon in the blood. This hormone antagonizes the insulin action, converting the hepatic glycogen storage to glucose that is released into the bloodstream. Beta cells are, then, forced to produce constantly insulin to lower the blood glucose concentration which leads to their dysfunction in the long term. Around 51% of male and 64.5% of female patients with glucagonoma develop diabetes (Song et al., 2018). Acromegaly is another health condition that cause insulin resistance and altered glucose metabolism. Adenomectomy often restores glucose levels in patients with the tumor suggesting that high amount of growth hormone is a risk factor for diabetes (Møller et al., 1992).

Drug-induced

Diabetes can also be a result of the action of specific drugs. These drugs can alter glucose homeostasis leading to hyperglycemia or hypoglycemia. The antibiotic Gemifloxacin, beta-

blockers, thiazide diuretics, corticosteroids, cyclosporine, tacrolimus, and protease inhibitors have been shown to raise blood glucose levels in patients with or without diabetes (Bangalore et al., 2007; Casula et al., 2017; Dehghani et al., 2020; Fathallah et al., 2015; Kowalchuk et al., 2021; Latek et al., 2019; Mamakou et al., 2018; Rehman et al., 2011; Sattar et al., 2010; Ställberg et al., 2020). 3-17% of people treated with protease inhibitors develop hyperglycemia due to the development of a body stress response leading to a decreased sensitivity to insulin and, consequently, diabetes (Rehman et al., 2011). 1.5-2.5% of patients with inflammatory and obstructive pulmonary diseases treated with corticosteroids develop hyperglycemia due to a reduced action of insulin and increased gluconeogenesis by activation of Phosphoenolpyruvate carboxykinase (PCK) gene transcription. Pentamidine is an anti-fungal/protozoal drug and its use as therapeutic agent has been associated with beta cell destruction and diabetes (Rehman et al., 2011).

Catamenial hyperglycemia

Catamenial hyperglycemia is a disorder related to menstrual cycle resulting in increased blood glucose levels (Gomez et al., 2017; Jamshed et al., 2013; Letterie & Fredlund, 1994). Catamenial hyperglycemia can develop into diabetic ketoacidosis (DKA) which is usually a consequence of T1DM (Gomez et al., 2017; Letterie & Fredlund, 1994). Then, in absence of T1DM, menstrual cycle alterations should be considered as cause of possible DKA. Glucose monitoring together with insulin release systems can be used to treat catamenial hyperglycemia and prevent serious complications in women.

Microvascular Complications

Diabetic retinopathy

Diabetic retinopathy (DR) is a common consequence of diabetes that affects the blood vessels of the retina with 93 million of people worldwide suffering from the disease (Yau et al., 2012). It is usually diagnosed 5 years after the symptoms begin and, if not cured, it can lead to loss of vision (Lechner et al., 2017). DR results from the long-term effects of hyperglycemia on retinal capillaries promoting endothelial dysfunction, in particular microangiopathy and arterial stiffness. The disease has two main stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is the early stage of DR and is characterized by increased vascular permeability with small areas of balloon-like vessels in the retina and breakdown of the blood-retinal barrier (BRB). PDR is the advanced stage during which new blood vessels are formed to compensate for the inability of the swollen capillaries to bring blood to all retinal cells. These new vessels are vulnerable and can break causing vitreous hemorrhage and retinal detachment, all contributing to vision loss (Lechner et al., 2017; Moreno et al., 2013). DR is treated with diabetes management while advanced cases require laser therapy or surgery (Moreno et al., 2013).

Diabetic neuropathy

Diabetic neuropathy (DN) is one of the most dangerous complications of diabetes mellitus that can lead to death. Hyperglycemia can lead to neuronal damage altering several molecular pathways in neurons such as polyol and hexosamine pathways (Dewanjee et al., 2018). In particular, peripheral neuropathy affects 30-50% of people with diabetes and is usually classified as multifocal neuropathy. Symptoms include pain and numbness in legs and arms due to damage of the autonomic small fibers. It is usually diagnosed through the thermal threshold testing that evaluates how sensitive a person is to temperature changes. Patients with DN have usually a reduced ability to feel those changes (Dewanjee et al., 2018; Feldman et al., 2019; Malik, 2020). A valuable screening tool to identify patients with peripheral neuropathy is the neuropad test that measures the plantar sweat production. Abnormal results indicate sudomotor dysfunction possibly associated with peripheral neuropathy (Malik, 2020). Early

diagnosis of DN is useful to immediately start treatment and prevent damage of the large nerve fibers that can be deadly.

Diabetic nephropathy

Another common complication of type 1 and T2DM is diabetic nephropathy. It is characterized by the loss of kidney function, and it is one of the causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Papadopoulou-Marketou et al., 2017). Based on the extent of the glomerular, interstitial, and vascular lesions, diabetic nephropathy is characterized by four different stages. Diabetic nephropathy is mostly treated with antidiabetic medications. It is associated with an increased risk of death, in particular from cardiovascular disease.

Macrovascular Complications

Diabetes has several macrovascular complications (Viigimaa et al., 2020).

Cardiovascular disease

Diabetes has caused the death of 1.6 million people till now mostly due to associated cardiovascular diseases (Henning, 2018). Patients with diabetes and no myocardial infarction have a similar risk to develop acute coronary syndrome compared to nondiabetics that have had myocardial infarction. But the mortality rate for patients with diabetes after developing myocardial infarction is twice compared to the mortality rate of patients without diabetes (Htay et al., 2019). Risk factors for cardiovascular diseases in patients with diabetes are insulin resistance, hyperglycemia and excess free fatty acids that increase oxidative stress and disrupt protein kinase C (PKC) intracellular signaling which results in vascular swelling, constriction of blood vessels, thrombosis and atherogenesis (Htay et al., 2019). Interestingly, also hypoglycemia is associated with an increased risk of cardiovascular effects and mortality through several mechanisms. Patients with diabetes are subjected to hypoglycemic episodes and, consequently, they have a major risk to develop hypoglycemia induced cardiovascular effects (International Hypoglycaemia Study Group, 2019).

Cerebrovascular disease

Diabetes is an important risk factor for the development of cerebrovascular diseases and 20% of people with diabetes die from stroke (Georgakis et al., 2021; Phipps et al., 2012). Hemoglobin A1c (HbA1c), fasting glucose levels, insulin resistance and beta cell function parameters have been evaluated to investigate their association with several types of cerebrovascular diseases. In particular, high HbA1c levels, as well as insulin resistance and beta cell dysfunction are associated with an increased risk of ischemic stroke of large arteries and small vessels. Increased levels of Hb1Ac are also correlated with carotid atherosclerotic plaque formation, fractional anisotropy and white matter and brain atrophy markers confirming the close link between diabetes and cerebrovascular disease development (van Sloten et al., 2020).

Peripheral artery disease

Peripheral artery disease (PAD) is characterized by a reduced blood flow to the extremities of the body and is often caused by atherosclerosis, plaque formation in the vessel walls, that reduce the blood flow through them (American Diabetes Association, 2003). Since diabetes causes vascular dysfunction leading to vascular inflammation and atherosclerotic plaque deposition in the arteries, PAD is more common in patients with diabetes compared to non-diabetics (Barnes et al., 2020). Patients with both PAD and diabetes, especially those considered at high risk for foot ulcer development, have also an increased risk of lower extremities amputation (Firnhaber & Powell, 2019). Individuals belonging to minority groups: Native American, African American and residents of rural areas have also shown a higher risk of lower extremities amputation compared with whites, suggesting that a difficult socioeconomic environment influences the availability of appropriate health care tools favoring

drastic and irreversible medical interventions, such as leg amputation (Mascarenhas et al., 2014).

Conventional Therapeutic Approaches for Diabetes Management

Conventional therapies for diabetes can be split into four main categories: exercise and weight control, medical nutrient therapy, oral glucose drugs and insulin injections.

Exercise and Weight Control

Exercise has been shown to be beneficial in lowering glycemic blood levels in patients with diabetes (Ajala et al., 2013; Boulé et al., 2001). Different kinds of training, such as aerobic, resistance and combined, are effective in reducing HbA1c levels (Ajala et al., 2013; Boulé et al., 2001), suggesting that physical activity is as important as diet and medications in diabetes care. Diet is particularly important in weight control and a food approach with higher amount of proteins, lower amount of carbohydrates, lower glycemic index (similar to Mediterranean diet) reduces blood sugar levels in patients with diabetes at high risk of cardiovascular disease (Gregg et al., 2012). Such regime is more effective than all antidiabetic therapies in achieving non-diabetic fasting glucose levels in 50% of patients with long-duration T2DM (Lean et al., 2019). Intensive weight loss intervention based on physical activity, diet and social support is associated with remission of diabetes (Snowling & Hopkins, 2006; Steven & Taylor, 2015), underlying the importance of weight management in diabetes treatment.

Medical Nutritional Therapy

Medical nutritional therapy (MNT) is a personalized medical guidance for patients with diabetes. It is provided by registered dietitian nutritionists (RDN) and offers support a nutritional guideline for each patient. The RDN develops a nutritional diagnosis, goal, and care plan to help the patient to manage or treat diabetes (Evert et al., 2019). Behavioral and lifestyle changes are supported by repeated follow-up visits that involve monitoring and evaluating progress, as well as any health or medication changes. The eating plan is tailored for each patient taking in account his/her cultural, religious, and dietary beliefs (Evert et al., 2019). MNT has demonstrated its effectiveness in improving HbA1c levels and body weight control in type 1 and type 2 patients with diabetes (Franz et al., 2017; Morris & Wylie-Rosett, 2010). This kind of therapy is focused not only on treating diabetes but also other medical conditions, such as cardiovascular diseases, cancer, and kidney disease (Morris & Wylie-Rosett, 2010).

Oral Glucose Lowering Drugs

Oral drugs used to treat diabetes belong mainly to the following classes: biguanides, sulfonylureas, meglitinides and thiazolidinediones (Alam et al., 2019; American Diabetes Association, 2020; Holman et al., 2008; Home et al., 2009; Joshi et al., 2015; Kajbaf & Lalau, 2014; Leonard et al., 2018; van de Laar et al., 2005; Yin et al., 2014). Among those drugs, the thiazolidinedione, pioglitazone, has shown some medical concerns in several studies: it is effective in lowering fasting blood glucose and HbA1c levels but can cause edema and lead to body weight increase (Alam et al., 2019). Nevertheless, the drug is used by patients with diabetes, dyslipidemia and cardiovascular diseases. Sulfonylureas and metformin are associated with decreased risk of heart attack, diabetic complications, and death (Holman et al., 2008; Home et al., 2009; Kajbaf & Lalau, 2014; van de Laar et al., 2005; Yin et al., 2014). Although they have positive medical effects, sulfonylureas, such as glyburide, and metformin and have been linked to a higher risk of hypoglycemia compared to pioglitazone (Holman et al., 2008).

Insulin Injections

Insulin injections are the primary treatment for patients with T1DM who fail to naturally produce the hormone (Swinnen et al., 2009). Insulin therapy is less used for patients with T2DM and only when meal plan, exercise, weight loss and antidiabetic oral drugs do not achieve the desired reduction of blood glucose concentration (Hirsch et al., 1990; Swinnen et al., 2009). Insulin therapy is does not started immediately but when HbA1c levels are above 7% after at least 2 months of dual oral therapy. When this does occur, insulin administration is gradual and combined with other medications to ensure the best control of blood glucose levels. One insulin injection is usually not enough and multiple administrations per day are necessary to achieve and maintain HbA1c levels under 7% (Silver et al., 2018). Two possible side effects of insulin therapy include hypoglycemia and body weight gain. A successful insulin therapy requires that patients monitor their blood sugar levels at least four times a day and before every meal as well as control their food intake. If properly followed, this treatment reduces hypo and hyper glycemic episodes and can guarantee a long healthy life for patients with T1DM (Hirsch et al., 1990).

Recent Trends in Therapeutic Approaches for Diabetes Management

New Pharmacological Therapies

Dipeptidyl peptidase-4 (DPP-4) inhibitors

New pharmacological treatments for T2DM include drugs that inhibit the incretin hormone-regulator dipeptidyl peptidase-4 (DPP-4) and consequently lower the blood glucose levels (Ahrén et al., 2002; Aschner et al., 2006; Herman et al., 2006; Mu et al., 2006; Pratley et al., 2006; Raz et al., 2014; Rosenstock et al., 2019). The effects of the DPP-4 inhibitor, des-fluoro-sitagliptin, on beta cell mass and function, have been evaluated in a mouse model of T2DM, the high-fat diet (HFD) streptozotocin (STZ)-induced diabetic mouse that has defects in insulin sensitivity and secretion. After 2–3 months of treatment with this DPP-4 inhibitor, HbA1c, triglycerides, and free fatty acids levels were significantly reduced, as well as postprandial and fasting hyperglycemia. Beta cell mass and beta cell-to-alfa cell ratio were increased, together with insulin content and glucose stimulated insulin levels (Herman et al., 2006). The positive effects of DPP-4 inhibitors on glycemic control have been demonstrated also in patients with T2DM (Mu et al., 2006).

Another DPP-4 inhibitor, vildagliptin, has been tested in patients with T2DM who had previously been on a diet. This drug, as monotherapy, has been able to improve the glycemic control, beta cell function and HbA1c blood levels in those subjects (Pratley et al., 2006).

Glucagon-like peptide-1 (GLP-1) receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists belong to a new class of drugs used for type 2 patients with diabetes (Blonde & Russell-Jones, 2009; Diamant et al., 2014; Fadini et al., 2013; Samson & Garber, 2013; Toft-Nielsen et al., 1999; Zander et al., 2002). The safety and efficacy of those drugs have been evaluated in several clinical trials in which HbA1c and fasting blood glucose levels together with beta cell function were considered in placebo and treated groups. GLP-1 receptor agonists are able to lower the fasting plasma glucose levels, together with the free fatty acids and HbA1c levels over the course of 6 week treatment (Toft-Nielsen et al., 1999).

When given intravenously, GLP-1 agonists have been able to increase insulin and c peptide levels, reduce fasting plasma glucose concentration, and both systolic and diastolic blood pressure values in type 2 patients with diabetes over the course of 48 hours. No changes in free fatty acids and triglycerides levels have been observed in this study, suggesting that those can be achieved with a long-term GLP-1 receptor agonist treatment instead of a short-term administration (Zander et al., 2002). No side effects have been shown in those clinical

trials although more studies are needed to better evaluate the safety of those drugs (Toft-Nielsen et al., 1999; Zander et al., 2002).

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) are antidiabetic drugs as they favor glucose excretion via the urinary tract (Berhan & Barker, 2013; Bolinder et al., 2012, 2014; Scheen, 2015; Stenlöf et al., 2014). SGLT2 inhibitors, either as monotherapy or in combination with other antidiabetic drugs, are effective in lowering HbA1c levels, body weight and blood pressure in patients with T2DM although their use is associated with genital and urinary tract infections (Berhan & Barker, 2013).

A clinical trial has tested the long-term effects of dapaglifozin on blood glucose levels and body weight in patients with diabetes. The drug was able to improve the glycemic control, reduce weight and fat mass, and HbA1c levels without changes in bone turnover over the course of 102 weeks in patients with T2DM who experienced a poor glycemic control with metformin (Bolinder et al., 2014).

Rapid-acting insulin analogs

The development of insulin analogs has allowed to use therapeutic drugs that resemble more closely the physiological behaviour of human insulin. The pharmacokinetic and pharmacodynamic profiles of insulin analogs (lispro, aspart and glulisine) have been shown to be similar to human insulin but with faster onset and termination of action (Becker et al., 2005; Grunberger, 2014; Heinemann et al., 1996; Luijf et al., 2010; Mudaliar et al., 1999). Glargine and detemir, two basal insulin analogs, are reported to have a longer duration of action, less variability and greater predictability of effects, cause less hypoglycemia (particularly nocturnal) and are associated with less weight gain compared to other analogs (Grunberger, 2014). Although more expensive, those analogs show less risk of hypoglycemic episodes compared to normal human insulin, giving additional therapeutic benefits to patients (Grunberger, 2014).

The pharmacokinetics and pharmacodynamics of glulisine, lispro, and human insulin have been exhaustively evaluated in a study involving obese people. In this study, subcutaneous injections of each insulin (0.3 $U.kg^{-1}$) were given to nondiabetic volunteers in predetermined sequences (mean Body Mass Index (BMI) > 34 $kg.m^{-2}$). Glulisine and lispro were found to have faster onset of action together with higher fractional glucose infusion rates (GIR), both GIR-area under the curve (AUC) and maximal GIR values than conventional human insulin. They were able to stimulate also a faster glucose metabolism in individuals with less insulin resistance as measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA) index. Glulisine and lispro showed time to 20% and 80% of total GIR-AUC shorter than conventional human insulin, suggesting that those analogs have rapid and shorter pharmacokinetic profiles. Altogether, those data support a more rapid action profile of insulin analogs compared to human insulin regardless of BMI in obese patients (Becker et al., 2005).

Transplantation

Islet's Transplant

Islet transplant procedure is another therapeutic option in the treatment of diabetes (Farney et al., 2016; Lehmann et al., 2005; Nanji & Shapiro, 2006; Rickels & Robertson, 2019; Shapiro et al., 2000, 2005, 2006; Warnock et al., 2005). Allogenic transplantation remains a riskier procedure to perform compared to autologous islet transplantation, due to the implantation of foreign cells (allogenic) that can stimulate an immune foreign body response leading to the destruction of the islets and failure of the procedure (Farney et al., 2016). Microencapsulation of the islets as attempt to prevent the immune system mediated reject of the implant has shown harmful effects on both the islets and the patients. Different kind of encapsulation have been implemented in transplantation procedures: macroencapsulation

requires that multiple islets are incorporated in 1 or several large capsules as opposed to microencapsulation requiring 1 or 2 islets are incorporated in 1 microcapsule (Nanji & Shapiro, 2006; Warnock et al., 2005). As surface area expands at a lower rate than volume, diffusion of nutrients and oxygen are slower in the macrocapsules that have a higher surface area to volume ratio compared to microcapsules. Consequently, control of blood glucose concentration is different between macro and micro-capsules, with the latter favoring a faster exchange of insulin and glucose through the capsule wall and a steady glycemia management. For this reason, much attention has been paid towards microencapsulation as a better therapeutic option for patients with diabetes even if this has some challenges that have to be addressed, such as: internal oxygen and nutrients transfer limitation to encapsulated cells, reduction of total transplant volume, reduction of inflammatory response after transplant of encapsulated cells (Nanji & Shapiro, 2006; Warnock et al., 2005).

Although autologous islet transplantation is more successful, the allogenic transplantation can be beneficial for patients with severe hypoglycemia and patients taking already immunosuppressive drugs to support transplantation of other organs, such as kidney (Shapiro et al., 2000). In this regard, a study has shown that 7 patients with T1DM receiving islet allotransplants and taking glucocorticoid-free immunosuppressants such as sirolimus, tacrolimus, and daclizumab, have been insulin-free soon after the transplantation. Only 1 patient required islet cells from 3 different donors. Those results confirm the utility of allogenic islet transplantation for diabetes treatment (Shapiro et al., 2000).

Usually, 1/3 of recipients of auto-islets develop insulin independence as opposed to almost half of patients receiving allo-islet transplants. Anyway, only a small percentage (8%) of patients with T1DM who had received pancreatic islet transplants do not need insulin therapy after 1 year from the surgery, suggesting islet transplantation does not have long-term effects on diabetes management yet (Shapiro et al., 2000).

Pancreatic Transplantation

The American Diabetes Association (ADA) recommends pancreatic transplantation for patients with diabetes who receive also a kidney transplantation in order to avoid continuous injections of insulin ("Pancreas Transplantation for Patients with Type 1 Diabetes: American Diabetes Association," 2000). Double pancreas and kidney transplantation does not compromise patient survival and, in fact, improve the function of the transplanted kidney (Smail et al., 2012). In absence of kidney transplantation, ADA has also established eligibility requirements for only pancreas transplantation. For instance, if a patient has frequent, acute metabolic complications that require medical attention, he/she is eligible for a pancreatic transplant ("Pancreas Transplantation for Patients with Type 1 Diabetes: American Diabetes Association," 2000; Pfeffer et al., 1996). In absence of scientific data showing better results with islet transplantation, pancreas transplant remains the elective choice in the treatment of severe forms of diabetes. However, transplantation of the pancreas can also have some complications. Indeed, a study in patients who had pancreas and kidney transplants has shown that 1/3 of those patients had impaired glucose tolerance due to a reduced insulin secretory response at basal state and after intravenous glucose and glucagon stimulation (Smail et al., 2012). Thus, it is to be expected that some patients may suffer from impaired glucose tolerance post transplantation due to a number of factors such as rejection damage and ischemia (prior to transplantation). These factors have to be considered prior to performing the transplant and appropriate tests must be applied to ensure that complications are prevented in transplanted patients. Another clinical study has shown that post-transplant diabetes mellitus (PTDM) has developed in 17% of T1DM and in 45% of T2DM patients (Neidlinger et al., 2010). That is a significant percentage which indicates that there can be common risk factors amongst patients developing PTDM, such as high BMI (prior to transplant), high daily insulin doses (prior to

transplant) and acute rejection of the pancreas. Those risk factors can eventually lead to pancreatic malfunction and hyperglycemia (Dean et al., 2008; Neidlinger et al., 2010).

Bone Marrow Transplantation

Diabetes affects the differentiation of bone progenitor cells (Barman et al., 2019; Duan et al., 2019; Malerbi et al., 2017; Thakkar et al., 2015; Venkat et al., 2020; Voltarelli et al., 2007). It is known that diabetes is associated with persistent inflammation and accumulation of macrophages that impair wound healing processes (Barman et al., 2019). Consequently, bone marrow transplantation can have some adverse effects and should be carefully considered in patients with diabetes. Of course, immunosuppressive drug treatment increases the success of the hematopoietic stem cell transplantation as therapy forT1DM , even if a long-term insulin independence is not guaranteed (Voltarelli et al., 2007). Transplantation of exosomes from bone marrow stromal cells to diabetic mice suffering a stroke has shown multiple positive effects, such as improvement of blood brain barrier by enhanced tight junction protein function, increased axon and myelin density associated with increased number of oligodendrocytes and their progenitor cells, decreased macrophage and inflammatory factors activation.

Then, exosome transplantation increases neurorestoration and functional positive outcomes in mice suffering from strokes and can be a promising treatment option for patients suffering from diabetes cardiovascular complications.

Future Perspectives

Pharmacological Therapy for Weight and Glucose Control

Peptide hormone combination therapies

The adipocyte-secreted hormone, leptin is a protein encoded by the obese (ob) gene and has a wide range of functions in the body: it influences several hypothalamic-pituitary endocrine axes, that regulate the function of adrenal and gonadal glands, pancreatic islets, and thyroid. The hormone exerts pleiotropic effects also on angiogenesis, immune system, osteogenesis, and wound healing (Clemmensen et al., 2014; Grasso, 2011). Several clinical trials have shown that the recombinant human leptin has positive effects on energy balance and obesity related endocrinopathies when used to treat rare kinds of human obesity caused by specific ob gene mutations (Moon et al., 2012).

Leptin has also potent anti-diabetic actions that are independent of its effects on body weight and food intake. In particular, it can reverse diabetes in animal models of both type 1 and T2DM. In addition, long-term leptin-replacement therapy is well tolerated and dramatically improves glycemic control, insulin sensitivity, and triglycerides levels in patients with severe insulin resistance (Moon et al., 2012). Those results have stimulated the creation of new anti-obesity and anti-diabetes treatments involving the development of leptin receptor antagonists, synthetic peptide analogs and mimetics (Moon et al., 2012). Those leptin analogs in combination with GLP-1 receptor agonists have shown positive effects on glucose and lipid metabolism in obese mice (Grasso, 2011).

Incretins combination therapy

A new peptide with agonist action at three peptide hormone receptors: GLP-1, glucose dependent insulinotropic polypeptide (GIP) and glucagon receptors has shown positive effects on body weight and diabetic complications prevention in rodent models of obesity (Finan et al., 2015). Dual co-agonists or best mono-agonists diabetic therapies are less effective in reducing body weight, improving glycemic control, or reversing steatosis in diabetes animal models compared to this triple co-agonist therapy. Genetic, pharmacological and selective chemical loss-of-function studies have validated the contribution of each of those molecules in metabolic changes *in vivo*. The metabolic efficacy of this kind of treatment is due to a synergistic combination of glucagon, GLP-1 and GIP that increases energy expenditure,

decreases caloric intake, and mitigates the diabetogenic effects of glucagon, respectively, improving glucose control (Finan et al., 2015). At the same time, researchers have developed a peptide that is a potent co-agonist of both receptors of the incretin hormones, GLP-1 and GIP. In comparison to other GLP-1 agonists, the antihyperglycemic and insulinotropic effects of this unimolecular dual incretin peptide are significantly improved not only in rodent and primate (cynomolgus monkeys) models of obesity and diabetes (diabetic (db/db) mice and Zucker diabetic fatty (ZDF) rats) but also in patients with diabetes. The dual incretin co-agonist is effective in reducing fat mass in obese rats, in contrast to selective GIP agonists that have little effect on weight loss. The site-specific lipidation (Polyethylene Glycol (PEG) ylation) of the protein leads to a prolonged duration of action and then, less dosing avoiding the adverse gastrointestinal symptoms caused by administration of high amount of selective GLP-1 agonists. Anyway, further studies are needed to confirm the potent effects of dual incretins agonists in the management of T2DM (Finan et al., 2013).

Gene Therapy

Gene therapy is a new form of treatment that focuses on altering genes or cells of the patient to achieve the desired goal. Gene therapy can be *ex vivo* or *in vivo*. *Ex vivo* therapy is based on taking the patient cells out of the body, modifying them genetically, and returning them back in the patient. *In vivo* therapy focuses, instead, on modifying the patient cells without removing them from the body.

Ex vivo therapy

Some of the first studies performed in the *ex vivo* gene therapy field have explored the ability of cells different from beta cells to produce insulin with the goal to implant them in the human body as additional source of the hormone (Fodor et al., 2007; Halban et al., 2001; Kuroda et al., 2011; Zalzman et al., 2003). Those experiments have been performed in rat liver cells (hepatocytes). Those cells were isolated from the rodents and, after culture with the insulin promoter factor 1, they were able to produce and release insulin in response to glucose and sulfonylureas. When implanted in diabetic mice, those cells were able to reduce the non fasting glucose levels in diabetic mice (Fodor et al., 2007).

Fetal human progenitor liver cells (FH) can also be induced to differentiate into insulin-producing cells after expression of the pancreatic duodenal homeobox 1 (Pdx1) gene, a key transcription factor in pancreatic development and insulin expression in beta cells. Those FH cells were able to produce and release insulin in response to glucose and maintain euglycemia for prolonged periods in diabetic mice, suggesting that this approach can be a novel source of cells for transplantation into patients with T1DM (Zalzman et al., 2003). When used for *ex vivo* gene therapy, cells must be engineered properly in order to adapt to physiological changes occurring in the body such as aging, fluctuations in weight, and body response to exercise, respond to glucose in order to avoid episodes of hypoglycemia and hyperglycemia and not stimulate the immune response that can cause rejection from the human body (Halban et al., 2001; Kuroda et al., 2011).

In vivo therapy

The liver is an organ of interest in the field of gene therapy as hepatocytes can be induced to differentiate in islet cells and used to replace faulty beta cells in the pancreas. For an *in vivo* gene therapy approach, adenoviruses have been used as vectors to carry the proinsulin gene in the liver of murine models ofT1DM . After the infection, those cells were able to secrete insulin under proper stimulation (Auricchio et al., 2002; Chan et al., 2003; Kojima et al., 2003; Morral et al., 2002). Those results have shown that hepatocytes can be used as an additional source of insulin after genetic manipulation even though they aren't naturally built to produce the hormone. Besides insulin, the enzyme GCK has been also overexpressed in the liver to evaluate the effects on insulin release and glycemic control (Morral et al., 2002; O'Doherty et al., 1999).

Genetic manipulation of the enzyme in diabetic rats has been able to decrease blood glucose levels by 38% and increase insulin concentration in the blood by 67% but had also a drastic effect on fat metabolism, increasing free fatty acids levels by 310% and triglycerides by 190% (O'Doherty et al., 1999). Those data have shown that genetic manipulation of hepatic GCK is still far from being considered as a valid approach to treat diabetes. On the other hand, expression of pdx1 in hepatocytes of diabetic mice has been able to increase plasmatic insulin levels by 300%, suggesting that genetic manipulation of this transcription factor can be considered to elaborate new antidiabetic strategies (Ferber et al., 2000).

Stem Cell Therapy

Stem cell therapy is one of the newest and most advanced approaches for the treatment of major metabolic diseases such as diabetes (Hori, 2009; Maehr et al., 2009; Meier et al., 2006; Millman & Pagliuca, 2017; Pagliuca et al., 2014; Spaggiari et al., 2009; Stock et al., 2020; Voltarelli et al., 2007). Stem cells are fast replicating cells that have the ability to differentiate into any type of cell in the body such as neuronal, muscle or pancreatic cells. The effects of stem cell therapy have been evaluated when a nonmyeloablative hematopoietic stem cell transplantation (AHST) has been used to cure T1DM in patients taking immunosuppressive drugs (Voltarelli et al., 2007). Stem cells were injected into patients intravenously and over the course of months. After 6 months from the transplantation, C peptide levels were increased, indicative of more insulin being produced. On the other hand, anti-glutamic acid decarboxylases (GAD) plasmatic levels, that are usually high in type 1 patients with diabetes and are indicative of an immune mediated destruction of beta cells, were reduced. Blood glucose levels were also reduced and HbA1c concentration was less than the 7%, confirming an improved beta cell function in those patients who did not require intensive insulin therapy anymore (Voltarelli et al., 2007). Stem cell transplantation has been effective in enhancing beta cell function but is not recommended in patients with diabetic ketoacidosis. Although stem cell therapy has proven effective in reversing hyperglycemia, most patients require insulin treatment or conventional antidiabetic therapy after some months from the transplantation due to a decline of beta cell mass over the time for the activation of the immune system (Meier et al., 2006). The immune mediated loss of beta cells can be avoided if the stem cells implanted in the patient are not from donors but derived from the same patient. In this perspective, stem cell therapy is focusing more on reprogramming the fibroblasts of patients with diabetes in induced pluripotent stem cells (iPS) that are forced to differentiate in beta cells that are then reimplanted in high vascularized body tissues of the same patient (Maehr et al., 2009; Millman & Pagliuca, 2017; Pagliuca et al., 2014). This approach has the potential to tailor the antidiabetic therapy to each individual reducing the risk of immune mediated rejection of foreign cells.

Smart Insulin-Delivery Technologies

Closed-loop glucose responsive insulin (GRI) delivery systems

Continuous glucose monitoring (CGM) (Hanna et al., 2020) together with a continuous subcutaneous insulin infusion pump (CSII), known as artificial pancreas or integrated closed-loop control (CLC), has been found to improve glycemic levels in T1DM patients (Breton et al., 2012; Thabit & Hovorka, 2016). Several efforts have been made to ameliorate the CLC. A clinical trial has compared two modular CLC constructs: a standard control-to-range (sCTR) and an enhanced control-to-range (eCTR). Those two systems were used by patients recruited by the Universities of Virginia, Padova and Montpellier during 22-hours hospitalization. Besides to decreasing hypoglycemia by 2.7-fold, sCTR enhanced the time the patients spent in near normoglycemia from 61% to 74%. With the eCTR, it was possible to achieve a higher time in near normoglycemia (97%) and a higher time with tight glycemic control (77%), and

to reduce the overnight variability in mean blood glucose levels without increasing hypoglycemia (Breton et al., 2012).

When comparing the pharmacokinetic properties of different insulin injections, such as Humalog (lispro) and ultra-rapid lispro (URLi), the latter has shown a faster onset of action, a reduced late exposure, and an overall shorter exposure length and a lower duration of action in patients with T1DM. Differently from Humalog, URLi had the same time-to-action profile in both old and young patients with T1DM and had also a major effect in reducing the postprandial glucose concentration, likely due to its ultra-rapid pharmacokinetic profile. Both Humalog and URLi are safe and well tolerated by patients with diabetes (Linnebjerg et al., 2020).

The artificial pancreas (or CLC) brings enormous benefits in glucose control and, in general, diabetes management to type 1 patients with diabetes with unmet clinical needs. The CLC differs from conventional, threshold and predictive low glucose suspension of insulin technology by delivering automatic correction boluses of the hormone based on real time glucose sensor readings. Consequently, CLC offers a tighter control of glucose levels with reduced risk of hypoglycemia, that it is particularly important for patients with diabetes as they require insulin doses that fluctuate daily between one-third and three-fold. Without any doubt, the use of the CLC system, under appropriate supervision or remote monitoring, is effective in treating T1DM in children, adolescent, and adults. Further innovation will guarantee the wider adoption of this system in a clinical setting (Thabit & Hovorka, 2016).

Polymer-based GRI systems

GRI systems are insulin devices or insulin formulations that guarantee the delivery of the hormone based on the blood glucose levels of the patients (Norrild & Eggert, 1995; J. Wang et al., 2020; Yang et al., 2019). Boronic acids have been studied as sugar sensors for years. Nuclear Magnetic Resonance (NMR) spectroscopy studies have shown the formation of complexes between aromatic boronic acids and D-glucose under neutral nonaqueous and alkaline aqueous conditions. Those complexes contain the furanose form of the glucose attached to two boronic acid groups and the binding site position for the second boronic acid varies according to the conditions (neutral non aqueous or aqueous alkaline) of the chemical reaction. Then, the capacity of boronic acid derivatives to bind glucose forming cyclic boronate esters has been exploited to create non-invasive glucose sensor devices that are used in the fields of diabetes diagnostics and therapeutics (Norrild & Eggert, 1995). But the interaction between certain molecules and glucose is also important to create glucose-responsive strategies for insulin delivery. For example, since glucose binds its transporter on the surface of erythrocytes (red blood cells (RBCs)), a delivery system containing a glucose derivative (glucosamine)-modified insulin bound to RBC membrane has been developed. In hyperglycemic conditions, those erythrocyte-mimicking nanovehicles (EM-NVs) allow a fast release of insulin and, consequently, a reduction of blood glucose levels. As EM-NVs have better blood circulation and immune evasion properties, they have the potential to replace the current insulin delivery systems and represent, then, a promising tool in treatment strategies for diabetes. Besides diabetes, they can have a wide range of other biomedical applications ranging from drug carriers to photosensitizers to vaccine formulations (Yang et al., 2019).

Insulin-lectin complexes

Over the course of the past two decades, concanavalin A (ConA) has been the object of studies in the glucose monitoring field for its property to bind carbohydrates (Ballerstadt et al., 2006). ConA-based affinity sensors can reliably measure glucose levels over lengthy periods of time and ConA-sugar modified insulin compounds can be used as delivery systems for the release of insulin in the body (Ballerstadt et al., 2006; Brownlee & Cerami, 1983).

In vitro experiments have shown that oligosaccharides, such as mannotriose and maltotriose, have high binding affinity for insulin and those sugar-insulin compounds have the same biological activity of insulin, leading to the same glucose disappearance rate (t1/2) (3.0

min). The lectin ConA binds reversibly those glycosylated insulin molecules. In the absence of glucose, insulin is not released by the sugar-insulin/lectin complexes but when the concentration of glucose starts to increase in the surrounding environment, insulin begins to be released proportionally (Brownlee & Cerami, 1983). Despite the increasing interest in this lectin, some safety concerns about its toxic properties have been raised making its use in sensors or carrier systems for the human body limited (Ballerstadt et al., 2006; Brownlee & Cerami, 1983).

Glucose-responsive polymers

As insulin infusion is the central component of diabetes treatment, more and more efforts have been directed to ameliorate the drug delivery systems (DDS) in order to guarantee an accurate control of blood glucose levels through a consistent release of insulin (Anirudhan et al., 2016; Gu et al., 2013; Jin et al., 2009; Taylor et al., 2020; Yesilyurt et al., 2016). A graft copolymer of Oleic acid and β-cyclodextrin (OA-g ACD), coated with glucose oxidase (GOx) and catalase, has been described as potential glucose sensitive DDS (CAT). The swelling size of this nanoparticle was proportional to glucose concentration and after 240 minutes of exposure to glucose, the insulin release profile from the delivery system has shown a cumulative release of 78.0%, suggesting the copolymer is a good candidate to be used to administer the hormone intravenously (Anirudhan et al., 2016). A copolymer of methanol, 3-acryl aminophenylboronic acid and maleimide-glucosamine used to form glucose-sensitive nanoparticles (NPs) has shown similar positive effects in controlling insulin release based on glucose concentration (Gu et al., 2013).

Several injectable microgels have been studied to allow a better release of insulin in response to different concentrations of glucose. One of those systems is represented by monodisperse microgel (around 256 um) containing a pH-responsive chitosan matrix, enzyme nanocapsules, and recombinant human insulin. The nanocapsule protects the glucose-specific enzyme from denaturation processes and immune response when used in the host body. The microgels that is engineered to release insulin at basal rates under normoglycemia and at higher rates under hyperglycemia, has been effective in controlling the glycemic values more efficiently than other delivery systems in a mouse model of T1DM (Jin et al., 2009).

Needle-free delivery of insulin is an attractive alternative to subcutaneous injections of the hormone conventionally used to treat diabetes. For this reason, gelatinous materials are tested for the oral and transdermal release of insulin. Gelatinous formulations, such as phenylboronic acid-modified polyethylene glycol macromonomers, are good candidates to be insulin carriers as they are often biocompatible and biodegradable, maintain solubility and can provide protection from gut enzymes, making their oral administration possible (Taylor et al., 2020). Recent developments in the field of gel-based delivery systems are allowing also to address the closed loop control need to strictly maintain glycemic values within a narrow physiological range and avoid hypoglycemic episodes in patients with diabetes (Yesilyurt et al., 2016).

Intrinsic GRI systems

Insulin fusion proteins

One example of insulin fusion protein is represented by the insulin glargine. It is a biosynthetic human insulin that has a glycine instead of asparagine in position 21 of the alpha chain and two additional arginine residues at the carboxyterminal extension of the beta chain of the insulin molecule. The presence of small quantity of zinc in the formulation prolong the absorption into the bloodstream through the subcutaneous tissue. Insulin glargine has a delayed beginning and longer duration of action, and a flatter time-action profile compared to neutral protamine hagedorn (NPH) insulin. In combination with short-acting insulin, it is more effective than multiple injections of NPH plus short acting insulin in improving glycemic control and reducing the risk of hypoglycemia, especially at night, in people with T1DM. As

monotherapy or in combination with oral hypoglycaemic medications, insulin glargine reduces HbA1c and fasting blood glucose levels in patients with insulin-dependent or non-insulin-dependent T2DM (Gillies et al., 2000). After the development of insulin glargine, other insulin fusion proteins, that are responsive to glucose, have been evaluated. One of those hybrid protein is the insulin linked to the enzyme glucose oxidase via a disulfide molecule, 5,5'-dithiobis (2-nitrobenzoic acid) that is able to release different amount of insulin according to the levels of glucose in the surrounding environment (Ito et al., 1994).

Modified insulin derivatives

The pharmacokinetic properties of insulin can be modified by chemical or genetic changes in its structure. Some of those chemical modifications, such as the incorporation of an aliphatic or phenylboronic acid moieties, are able to increase the long-lasting and glucose-responsive characteristics of insulin, respectively. Those synthetic insulin derivatives allow a rapid reversal of blood glucose after glucose challenge in animal models of T2DM (Chou et al., 2015). The development of a GRI that responds to changes of blood glucose levels has been a long-standing objective. Hydrazone and thiazolidine based cleavable linkers are potential successful strategic tools to create GRI systems as they have almost no spontaneous hydrolysis that, on the other hand, increases with higher concentrations of glucose in the surrounding environment. Lipidated hydrazone and thiazolidines can be attached to the LysB29 side chain of insulin. In presence of glucose, those linkers hydrolyze, releasing active insulin from circulating deposits as demonstrated in vitro and clamp studies (Mannerstedt et al., 2021). Another GRI derivative is the phenylboronic acid (PBA)-insulin that contains a PBA attached to the LysB29 side chain of insulin as a diol binding element for carbohydrates. When glucose levels increase the PBA-insulin complexes dissociate releasing insulin from the bloodstream hormone deposits (Wu et al., 2013).

The field of insulin derivatives is in continuous development as it has the potential to offer immediate benefits to the patients, such as a better control of blood glucose levels and a reduced number of insulin injections resulting in an improved quality of life.

Glucose-regulated conformational changes

The glucose-regulated conformational changes insulins are potential derivatives that pass from an inactive to an active state after glucose binds to them. Advances in synthesis methodology have allowed bioactivity studies on new insulin analogs with a fourth disulfide bond showing that structural changes of native insulin can be exploited to regulate its function (Brunel et al., 2019).

X-ray crystallography and mutagenesis studies have suggested that the native state of insulin is inactive and, upon binding with its receptor, the hormone changes its conformation becoming activated. Experiments involving an A-chain analog of the insulin lacking the A6-A11 disulfide bridge have shown that the N-terminal alpha-helix domain of the A-chain reorganizes upon receptor binding, regulating the activity of the hormone. In fact, the analog has low biological activity suggesting that structural alterations in this part of the hormone can be used to create insulin derivatives that changes activity upon binding with a ligand (Hua et al., 1996).

To identify potential conformational switch sites for GRI design, DiMarchi *et al.* have analyzed 6 specific conformations of the receptor binding site of the insulin analog (*des*-[B29,B30]-Lys^{B28}-) insulin deriving from the manipulation of the 4 disulfide bridges in the molecule. The A8–B10 or A14–B10 disulfide bridge altered the central B-chain α-helix and N-terminal A-chain α-helix blocking the conformational switch that makes insulin active after binding to its receptor. Displacement of those imposed bridges by glucose relieves the alteration in the molecule and restore the activity of the hormone. Further structural studies are needed to synthetize more advanced insulin analogs that will have a better impact on patients with diabetes' health (Zaykov et al., 2014).

New Strategies in Diabetes Care

Multidisciplinary approach and telemedicine

Internet-based diabetes care has been under investigation cause of the potential to be a practical and cost-effective chronic illness self-management strategy (American Diabetes Association, 2021). A clinical trial lasted 12 months has assessed the positive effects of an Internet-based diabetes self-management program on diet, exercise, medication (primary outcomes), HbA1c, BMI, cholesterol, blood pressure values (secondary outcomes) in a court of patients with diabetes. Web-based interventions have been able to improve fat intake, eating habits and physical activity with small changes in the biological parameters of patients with diabetes, suggesting that this strategy integrated in the primary care can have a significant impact on public health thanks to its wide reach and easiness to assess (Glasgow et al., 2012).

Telemedicine has been introduced as a method to allow all patients, especially those in rural locations, to have equal access to health care. In particular, the Clinical Video Telehealth (CVT) is a real-time, pharmacist led CVT program designed to improve chronic disease management that has been used to evaluate changes in health conditions of Veterans at the Tennessee Valley Healthcare System.

Clinical pharmacy specialists (CPS) at the main facilities and community-based outpatient clinics (CBOC) were instructed to provide clinical pharmacy services to patients. One of the CPSs at the main hospital delivered services via telemedicine to the CBOCs where on-site clinical services were not available. CVT services by the CPS resulted in significant reduction of HbA1c values, and increased percentage of patients meeting the treatment goal for HbA1c levels established by ADA. The overall patient satisfaction scores were also high suggesting that CVT program is successful in improving health conditions of patients with diabetes (Maxwell et al., 2016).

Conclusion

In 2021, we celebrated the 100th birthday of insulin, whose discovery has changed the lives of millions of patients with diabetes. The advancement of new strategies to tackle diabetes has delivered optimistic outcomes and liberated the patients from their daily struggles associated with this disease. We are herein highlighting the most important aspects related to diabetes, such as the major types of the disease and their physiology. In addition, we are shedding lights on the different types of therapeutic approaches used as treatments for diabetes and the future therapeutic perspectives. Thus, a better understanding of the physiology and pathophysiology associated with diabetes mellitus would ensure the development of safe, effective and long-lasting therapeutic options.

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Abbreviations

Deoxyribonucleic Acid (DNA), Cytosine and Guanine separated by a phosphate (CpG), Gestational Diabetes Mellitus (GDM), Glucokinase (GCK), Maturity Onset Diabetes of the Young (MODY2), Permanent Neonatal Diabetes Mellitus (PNDM), Hepatocyte Nuclear Factor 1α (HFN1α), Insulin Promoter Factor 1 (IPF1), Neurogenic Differentiation 1 (NEUROD1), Berardinelli-Seip Congenital Lipodystrophy 2 (BSCL2), Phosphoenolpyruvate Carboxykinase (PCK), Ketoacidosis (DKA), Diabetic Retinopathy (DR), Non-Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR), Blood-Retinal Barrier (BRB), Diabetic Neuropathy (DN), Chronic Kidney Disease (CKD), End-Stage Renal

Disease (ESRD), Protein Kinase C (PKC), Hemoglobin A1c (HbA1c), Peripheral Artery Disease (PAD), Medical Nutritional Therapy (MNT), Registered Dietitian Nutritionists (RDN), Dipeptidyl Peptidase-4 (DPP-4), High-Fat Diet (HFD), Streptozotocin (STZ), Glucagon-Like Peptide-1 (GLP-1), Sodium-Glucose Cotransporter 2 (SGLT2), Body Mass Index (BMI), Glucose Infusion Rates (GIR), Area Under the Curve (AUC), American Diabetes Association (ADA), Post-Transplant Diabetes Mellitus (PTDM), Obese (ob), Glucose Dependent Insulinotropic Polypeptide (GIP), Diabetic (db/db), Zucker Diabetic Fatty (ZDF), Polyethylene Glycol (PEG), Fetal Human progenitor liver cells (FH), Pancreatic Duodenal Homeobox 1 (Pdx1), Hematopoietic Stem cell Transplantation (AHST), Glutamic Acid Decarboxylases (GAD), Induced Pluripotent Stem Cells (iPS), Glucose Responsive Insulin (GRI), Continuous Glucose Monitoring (CGM), Continuous Subcutaneous Insulin Infusion (CSII), Closed-Loop Control (CLC), Standard Control-To-Range (sCTR), Enhanced Control-To-Range (eCTR), Ultra Rapid Lispro (URLi), Nuclear Magnetic Resonance (NMR), Red Blood Cells (RBCs), Erythrocyte-Mimicking Nanovehicles (EM-NVs), Concanavalin A (ConA), Drug Delivery Systems (DDS), Oleic acid and β-cyclodextrin (OA-g ACD), Glucose Oxidase (GOx), Catalase (CAT), Nanoparticles (NPs), Neutral Protamine Hagedorn (NPH), Phenylboronic Acid (PBA), Clinical Video Telehealth (CVT), Clinical pharmacy specialists (CPS), Community-Based Outpatient Clinics (CBOC**)**

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