



Next Generation Health Technology Assessment to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe

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EXECUTIVE SUMMARY

Diabetes mellitus (DM) is a metabolic disease characterized by an elevation of the blood glucose levels that occurs due to deficiencies in the insulin production or insulin sensitivity. If left untreated, it can cause several chronic and acute complications. Type 1 and type 2 DM are the most frequent types of diabetes. Type 1 DM (T1DM) is typically associated with failure in insulin production resulting from the destruction of pancreatic β -cells by T-cell-mediated autoimmunity. Type 2 DM (T2DM) is primarily associated with insulin secretory defects related to inflammation and metabolic stress among other contributors, including genetic factors.

DM is a complex disease which requires continuous medical care with multifactorial risk-reduction strategies. Frequent self-monitoring of blood glucose levels, self-management and education are essential to prevent acute complications and reduce the risk of long-term complications. DM needs to be managed in a long-term basis following different sequences of treatment, mainly pharmacological, but also considering nutritional and lifestyle recommendations. The diabetes epidemic has led to constant development of disease-controlling drugs and optimized treatment strategies to prevent disease progression and associated complications.

The choice of pharmacological agents for each patient should be a shared decision-making process that consider factors such as potential side effects, potential benefits, glucose lowering efficacy, dosing regimen or existing complications.

Pharmacologic therapy for DM can facilitate excellent glycemic control. Injected insulin and oral antihyperglycemic agent (OAA) therapy are the main alternatives. Non-pharmacological treatments, consisting of lifestyle changes such as diet and exercise, can be considered as a mechanism to treat the disease and improve the future prognosis. They have shown benefits in the management of T2DM and T1DM, as well as in future complications related to the disease.

The use of medical devices can complement treatment pathways and contribute to improve diabetes control. Continuous glucose monitoring systems are a complementary tool to blood glucose monitoring. For the last decade, they have been introduced into clinical practice offering more detailed information about trends, magnitude, duration, or fluctuations of glucose levels over the course of the day. For T1DM, continuous subcutaneous insulin infusion systems have shown to improve glycemic control.

This document contains a review on pharmacologic therapy pathways, lifestyle interventions and medical devices to treat patients with type 1 and type 2 diabetes mellitus.



INTRODUCTION

Diabetes Mellitus (DM) is a chronic condition that appears when the pancreas does not produce any or enough insulin or when the body cannot effectively use the insulin it produces (International Diabetes Federation, 2019). It is the direct cause of various short and long-term complications, which reduce the quality of life and increase the diabetes related morbidity and mortality. The disease is characterized by high blood glucose levels in fasting situations that appear to be associated with alterations in the metabolism of carbohydrates, fats and proteins. The most common types of diabetes are type 1 and type 2 DM.

Type 1 DM (T1DM) is typically associated with failure in insulin production resulting from the destruction of pancreatic β -cells by T-cell-mediated autoimmunity. It is the earliest-onset clinical form of diabetes and needs to be treated with exogenous insulin due to the deficiency or absence of synthesis of this hormone in the pancreas. The onset of this form of diabetes predominates in children and young people and it usually occurs before the age of 30. T1DM represents 5-10% of all diabetes cases. The incidence of T1DM is subject to wide geographic variations. Europe has the highest number of children with T1DM compared with the other the regions of the International Diabetes Federation (IDF) (approximately 140,000) (WDF, 2020). The region also has one of the highest incidence rates of T1DM in children, with an estimated 21,600 new cases per year. Finland has the world's highest incidence of T1DM in children with 62.3 new cases per 100,000 children each year (WDF, 2020).

Type 2 DM (T2DM) is the consequence of a deficit in insulin action due to alterations in the cell surface or in its interior, a deficit in insulin secretion or a combination of both. It is the most frequent form of diabetes, and it accounts for 90-95% of all diagnosed diabetes cases (American Diabetes Association, 2009). T2DM is associated with a strong genetic predisposition and the age of onset occurs after 40 years, although there are earlier forms of onset. 80-90% of people with T2DM are obese (American Diabetes Association, 2009). Excessive food intake causes an increase in resistance to insulin, being a very important factor for the development of T2DM.

In T2DM insulin treatment is not necessary for all patients, although there are specific cases in which, given high-risk situations for patient survival, insulin treatment is necessary.

On the other hand, this form of diabetes can take years to be diagnosed because hyperglycemias develop gradually, and the patient does not have the typical symptoms of the disease in the early stages. For this reason, 20% of patients diagnosed with T2DM already have evidence of chronic complications at the time of diagnosis (American Diabetes Association, 2009). The risk of developing this type of diabetes increases with age, obesity, and a sedentary lifestyle.

T2DM prevalence has nearly doubled since 1980, affecting 9.3% of the adult population in 2019, with half of the cases estimated to be undiagnosed, and this accounts for nearly 463 million worldwide (Saeedi et al., 2019). According to the International Diabetes Federation (IDF), over four million people died of diabetes and its accompanied diseases in 2019 (IDF, 2019).

Europe has the second least number of adult patients with diabetes among the regions of the IDF (6.8%). The intracontinental differences are extensive, ranging from 2.1% in Greenland to 11.1% in



Turkey. The diabetes epidemic has led to constant development of disease-controlling drugs and treatment strategies, generating rapid changes in national and international guidelines (IDF, 2019). The aim of this review is to summarize the current treatment options for T1DM and T2DM including pharmacologic treatment and different treatment combinations, non-pharmacologic treatment, and medical devices which contribute to improve diabetes control.

GLYCEMIC CONTROL

The reference standard in the global assessment of glycemic control of diabetes is the determination of glycated hemoglobin or hemoglobin A1c (HbA1c). HbA1c levels depend on the glucose concentration in the body for the last 90-120 days. When blood glucose levels are high, glucose adheres to structural and circulating proteins. HbA1c measures the degree of glucose in hemoglobin expressed as the total percentage of glycated hemoglobin concentration. The higher the percentage of glycated hemoglobin, the higher the patient's blood glucose levels in the past 90-120 days (Kilpatrick, 2008). Glycation of hemoglobin occurs during the 120 days of life of red blood cells, but the most recent glycemia levels have a greater influence on the HbA1c value. Theoretical models suggest that a patient with stable glycemic control will form 50% of his/her HbA1c in the month before the sample, 25% the month before and the remaining 25% between two and four months before (Tahara & Shima, 1995).

The clinical utility of HbA1c as a tool to assess the risk of complications caused by diabetes was first demonstrated in the publication of the results of the "Diabetes Control and Complications Trial DCCT" (DCCT) (The DCCT Research Group, 1993) and "United Kingdom Prospective Diabetes Study" (UKPDS) (UK Prospective Diabetes Study (UKPDS, 1998). Both studies established the effect of intensive glycemic control compared with conventional control to avoid the development of microvascular complications in patients with T1DM and T2DM. The DCCT study showed that a relative reduction of 10% in HbA1c levels is associated with a reduction of more than 40% in the rate of development and in the progression of microvascular complications (Lachin et al., 2008). However, the clinical parameter for HbA1c does not provide information on the magnitude or frequency of fluctuations in blood glucose.

The DCCT and UKPDS studies (The DCCT Research Group, 1993; UK Prospective Diabetes Study (UKPDS), 1998) have established targets for HbA1c levels in T1DM and T2DM. However, since the relationship between HbA1c and the risk of microvascular complications is exponential and there is no obvious threshold value, there are different criteria for the minimum recommended value of glycated hemoglobin to achieve a good glycemic control. Current clinical guidelines in UK (NICE, 2015a) suggest HbA1c target values lower than 6.5% in T1DM and T2DM for adults managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia (NICE, 2015b). For adults with T2DM on a drug associated with hypoglycemia, the recommended target value of HbA1c is 7.0% (NICE, 2015b). The American Diabetes Association considers that adult non-pregnant patients with diabetes achieve a good glycemic control when Hb1Ac is lower than 7%. HbA1c levels < 7% have shown to reduce the incidence of microvascular and neurological complications in T1DM and T2DM. Achievement of lower HbA1c levels (such as 6.5%) may be acceptable if this can be achieved safely without significant hypoglycemia or other adverse effects of



treatment. Less stringent HbA1c goals (such as 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications (American Diabetes Association, 2020). When the established HbA1c goals are not achieved but the preprandial glycemia (before meal intake) is within normal ranges, the objective is to maintain the postprandial glycemia (from one to two hours after a meal) within the established range.

PHARMACOLOGIC TREATMENT

Hypoglycemia is one of the major risk factors that need to be considered when combinations of multiple medications are used concomitantly. The choice of which pharmacological agent to use should be a shared decision-making process. The costs, potential side effects, potential benefits, glucose lowering efficacy and dosing regimen need to be taken into consideration before selecting a medication. Dosage adjustments are necessary for renal impaired patients. Regular monitoring is essential for all patients on pharmacological agents (Tan et al., 2019).

Each medication classes has a different mechanism of action and different molecular interactions, and consequently, different genetic variants that affect function. Studies of the genetic variants that can alter response to oral diabetes medications have generally shown modest effects, some of which are contradictory (Kleinberger & Pollin, 2015). Regardless, these studies represent findings that could provide information about future pharmacogenetic recommendations for oral DM medications.

The etiology-specific treatment recommendations for monogenic diabetes provide a current model of genetic diagnosis to pharmacological treatment that can be used for future implementation of pharmacogenetic findings into clinical recommendations (Kleinberger & Pollin, 2015).

Pharmacologic therapy for DM can facilitate excellent control, with the potential for normalization of HbA1c by insulin and a reduction in HbA1c of 0.5% to 2% for oral antihyperglycemic agent (OAA) therapy depending on the agent or agents used (Odegard & Capoccia, 2007).

The value of pharmacologic therapy in achieving and maintaining DM control has clearly been established. Pharmacologic treatment improves HbA1c levels, moreover, several well-designed trials have explored the benefit of pharmacologic therapy in improving avoidable and costly microvascular and macrovascular outcomes of DM (Odegard & Capoccia, 2007).

A variety of medications are available for treating T1DM and T2DM, each with different efficacy and side-effect profiles, and often with different modes and frequencies of administration. Treatment is selected and individualized based on specific patient requirements for glycemic control, and patient preferences, characteristics, and susceptibilities to side effects (Clifford et al., 2014).

Patients with T1DM require the exogenous administration of subcutaneous insulin therapy to maintain glycemic control. Furthermore, as it is a progressive disease with decline of pancreatic beta-cell function over time, most patients with T2DM will also eventually require insulin therapy (Clifford et al., 2014).



Historically, pharmacologic therapy for T2DM has been initiated when lifestyle modifications of nutrition and physical activity have either failed or are not producing adequate results in the lowering of HbA1c levels. Only in individuals who seemed reticent or were unable to make a lifestyle change or in individuals who had symptomatic hyperglycemia at diagnosis, pharmacologic therapy for DM was initiated at diagnosis (Odegard & Capoccia, 2007).

In August 2006, the American Diabetes Association (ADA) stated a change to this standard of practice with the recommendation to initiate metformin in all patients with T2DM at diagnosis along with appropriate lifestyle modifications and if there are no contraindications to the use of metformin. In addition to metformin, there are several pharmacologic options for the treatment of T2DM including oral agents, injected insulin, and, more recently, inhaled insulin (Odegard & Capoccia, 2007).

Insulin

Introduction

Insulin injection remains the main treatment for T1DM where insulin deficiency is observed (Tan et al., 2019). The use of insulin is essential for physiologic insulin replacement (Odegard & Capoccia, 2007). In order to prevent long-term complications, T1DM patients require intensive insulin regimen to achieve tight diabetes control (Dzygało et al., 2015).

T2DM often requires treatment intensification to maintain adequate glucose control, due to the gradual decline of beta cells' function. Insulin therapy is frequently needed after the failure of several oral glucose-lowering medications to reach and maintain HbA1c targets (Maiorino et al., 2019). When oral hypoglycemic drugs are not successful in regularizing glucose and HbA1c levels in T2DM, insulin can be utilized as monotherapy or together with oral hypoglycemic agents. The limiting factor of insulin is that it has to be administered through injections (Tan et al., 2019).

Currently, insulins used are either human insulin and/or analogs of human insulin. Since the introduction of insulin analogs in 1996, insulin therapy options for T1DM and T2DM have expanded. Insulin therapies are now able to more closely mimic physiologic insulin secretion and thus achieve better glycemic control in patients with diabetes (Donner & Sarkar, 2019).

Insulin types

The onset, peak, and duration of effect vary among insulin preparations. Insulin pharmacodynamics refers to the metabolic effect of insulin (Donner & Sarkar, 2019). Insulins are classified according to their type of action and they are categorized as rapid-acting, short-acting, intermediate-acting, and long-acting (Donner & Sarkar, 2019).

1. Rapid-acting analogs result from changes to the amino acid structure of human insulin which lead to decrease in hexameric insulin formation after injection into the subcutaneous (SQ) space. This leads to more rapid dissolution of insulin into monomers, more rapid insulin absorption into the bloodstream, and a shorter duration of action (Donner & Sarkar, 2019).

Examples of rapid-acting analog insulins are (Steele et al., 2008):



- Insulin Lispro (Humalog): results from the reversal of the B28 (proline) and B29 (lysine) amino acid sequence of insulin (Steele et al., 2008).
- Insulin Aspart (Novo Rapid): differs from human insulin by a substitution of the B28 amino acid proline with aspartic acid (Steele et al., 2008).
- Insulin Glulisine (Aspiara): differs from human insulin by changes in the amino acid asparagine at position B3 to lysine and the lysine at position B29 to glutamic acid (Steele et al., 2008).

Moreover, Technosphere insulin (Afrezza) is a type of inhaled insulin and its pulmonary absorption is faster than subcutaneously administered rapid-acting insulin preparations. In patients with T2DM, serum insulin levels rise within 5 minutes after inhalation and peak after 17 minutes (Donner & Sarkar, 2019).

2. Short-Acting Regular Insulin is injected pre-meal to blunt the postprandial rise in glucose levels. It forms hexamers after injection into the SQ space slowing its absorption. Hexameric insulin progressively dissociates into absorbable insulin dimers and monomers. For this reason, regular insulin has a delayed onset of action of 30-60 minutes and should be injected approximately 30 minutes before the meal to blunt the postprandial rise in blood glucose. Adherence to a 30-minute pre-meal schedule is inconvenient and difficult for many patients (Donner & Sarkar, 2019).

Short-acting insulin analogs provide rapid subcutaneous absorption, an earlier and higher insulin peak and more rapid post-peak decreases than human insulin (Shafie et al., 2017).

3. Intermediate-Acting Insulins: Neutral Protamine Hagedorn (NPH) is an insulin, whose onset of action is approximately 2 hours, peak effect is 6-14 hours, and duration of action of 10-16 hours (depending on the dose). Because of its broad peak and long duration of action, NPH can serve as a basal insulin only when dosed at bedtime, or a basal and prandial insulin when dosed in the morning. NPH insulin is available in various combinations with either regular insulin or rapid-acting insulins (Donner & Sarkar, 2019).
4. Long-acting insulins provide basal insulin coverage. Basal insulins suppress hepatic gluconeogenesis to prevent glucose levels from rising during the fasting state in insulin-deficient patients. Among patients with T1DM, basal insulins additionally prevent ketogenesis (Donner & Sarkar, 2019).

Long-acting insulin analogs maintain the basal level of insulin, are peakless compared with intermediate-acting human insulin and are therefore associated with a lower risk of nocturnal hypoglycemia (Shafie et al., 2017).

Examples of long-acting analog insulins are (Steele et al., 2008):

- Insulin Detemir (Levemir): has an amino acid modification and a fatty acid chain added to enhance formation of hexamers and increase binding to albumin. It is slowly absorbed from the injection site and, once in the circulation, insulin detemir slowly dissociates from



albumin (Waller & Sampson., 2018).

- Insulin Glargine (Lantus): has two amino acid changes that make the molecule more soluble at acid pH, and less soluble at physiological pH. It precipitates after subcutaneous injection, slowly redissolves and is then absorbed (Waller & Sampson., 2018).
- Insulin Degludec (Tresiba): has a single amino acid change and is conjugated to hexadecanedioic acid, which forms multi-hexamers in subcutaneous tissue and delays absorption (Waller & Sampson., 2018).

Antihyperglycemic treatment

Introduction

As new classes of medications have become available for the treatment of diabetes, clinicians and patients have faced an array of oral medications with different mechanisms of action. The first oral diabetes medications were sulfonylureas, which were introduced into the market in 1955. The second-generation sulfonylureas, which are still used today, were introduced in 1984. Metformin (a biguanide) was introduced in 1995, meglitinides in 1997, and thiazolidinediones in 1999 (Bolen et al., 2007).

Generally, clinicians must choose between older, less expensive medications such as a second-generation sulfonylurea or metformin and the newer, more expensive medications such as a thiazolidinedione or meglitinide. In addition, clinicians must consider concerns about specific medications conferring excess cardiovascular risks when compared with other oral diabetes medications or placebo (Bolen et al., 2007).

Many of those oral medications are available for the treatment of T2DM, including dipeptidyl peptidase-4 (DPP-4) inhibitors. Moreover, the diabetic market of injectable agents is also expanding, including the families of glucagon-like peptide-1 (GLP-1) analogs. The use of these drugs is projected to increase given the progressive ageing of the population, the rising number of medications that are currently available to treat hyperglycemia and the need to achieve and maintain therapeutic goals over time (Esposito et al., 2012).

Moreover, many of those oral medications may also be of benefit in T1DM, in addition to insulin, although many of them have not yet been approved for this indication (Fattah & Vallon, 2018).

Sulfonylureas

Sulfonylureas are secretagogues which work by triggering endogenous insulin secretion from pancreatic β -cells. It mainly targets the ATP-sensitive potassium channels on β -cells and is only effective in the presence of residual pancreatic β -cells (Proks et al., 2002). Sulfonylureas are recommended as initial treatment in the management of T2DM (Filion et al., 2019).

The main types of sulfonylureas include glimepiride, glyburide (glibenclamide) and glipizide (Vijan, 2015). There are no significant differences between the different sulfonylureas that allow recommending one over another (Sescam, 2020). In placebo-controlled clinical trials, glibenclamide, glipizide, and glimepiride have been shown to be equivalent (Zimmerman, 1997).



The main disadvantages of sulfonylureas are that they do not have any longstanding protective effects on β -cell functions and may speed up β -cell failure (Sola et al., 2015). After the initial drop in glucose levels, HbA1c concentrations have been shown to increase. There have been a great number of incidences where sulfonylureas cause hypoglycemia, especially from the older generation drugs (Schopman et al., 2014). Blood glucose concentrations can be lowered by almost 20%, whereas HbA1c levels can drop by 1%-2%. The unwanted side effect of sulfonylureas is the weight gain (Roumie et al., 2012).

Biguanides

Metformin is the most prescribed antidiabetic drug, especially used in obese and overweight individuals. This drug is still the best choice for monotherapy. It functions by increasing insulin sensitivity, boosting the uptake of glucose by phosphorylating GLUT enhancer factors and suppressing hepatic gluconeogenesis. Metformin can aid in losing weight and shows reasonable triglyceride and serum LDL cholesterol reduction (Lin et al., 2018). Metformin also functions by activating one of the enzymes involved in expressing hepatic gluconeogenic genes, known as AMP-activated protein kinase, in addition to inhibiting mitochondrial complex 1 and enzyme, glycerophosphate dehydrogenase in the mitochondria (Rena et al., 2017). All these lead to the lowering of glucose as well as HbA1c levels (Tan et al., 2019).

Furthermore, metformin is the first-line oral medication for T2DM because of its safety profile as an insulin-sensitizing agent (Kleinberger & Pollin, 2015) that works by increasing the glucose uptake variably in the muscle through amplification of the glucose transporters 4, and reduced hepatic glucose production, thus improving tissue sensitivity to insulin (Al Khalifah et al., 2017).

Therapy in T2DM is associated with decreased hepatic glucose production, decreased fasting plasma glucose, a reduction in HbA1c level, weight stabilization/loss, modest reductions in serum triacylglycerol, VLDL and LDL levels, as well as decreased C reactive protein, platelet activation and procoagulant factors (such as factor VII and fibrinogen) (Vella et al., 2010). Metformin therefore has properties that make it an attractive potential adjunct agent to insulin therapy in T1DM (Vella et al., 2010).

However, metformin does not affect β -cells and if there is no weight loss, insulin sensitivity in muscles do not show good progress, with HbA1c levels gradually rising again after the initial drop (Tan et al., 2019). It has a high variability of efficacy between patients, and it often needs to be supplemented with secondary agents (Kleinberger & Pollin, 2015).

Meglitinides

Meglitinides are another class of insulin secretagogues that also act by inhibiting the KATP channel to induce depolarization and insulin secretion. However, these medications act in a much shorter timeframe than sulfonylureas and consequently confer less risk of hypoglycemia. Meglitinides are rapidly metabolized by the liver. Meglitinide metabolism differs between repaglinide (by CYP2C8 and CYP3A4) and nateglinide (by CYP2C9) (Kleinberger & Pollin, 2015). While the chemical structures and mechanisms differ between these agents, the effect on early phase insulin release is similar, with a rapid rise in insulin concentrations after dosing and a short half-life. Early trial evidence supports their effect in reduction of postprandial glucose and reduction in hypoglycemic episodes (Black et al., 2007).



Although genetic variants in these metabolizing enzymes may alter pharmacokinetics of the medications, it does not appear to have major effects on the glucose levels of patients (Kleinberger & Pollin, 2015).

In T2DM, impairment of insulin secretion is an important component of the disease. The meglitinides are a class of oral antidiabetic agents that increase insulin secretion in the pancreas. The properties of this class of drug suggest that they have the potential to produce a rapid, short-lived insulin output (Black et al., 2007).

Meglitinides may offer an alternative oral hypoglycemic agent of similar potency to metformin and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated (Black et al., 2007). The main types of Meglitinides include repaglinide and nateglinide.

However, there is no evidence available yet to indicate what effect meglitinides will have on important long-term outcomes, in particular on mortality. The experience with meglitinides in terms of side effects is limited (Black et al., 2007).

Thiazolidinediones

Thiazolidinediones (TZDs) are PPAR (peroxisome proliferator-activating receptor) activators that act by improving insulin sensitivity and decreasing hyperglycemia by decreasing circulating free fatty acids (Kleinberger & Pollin, 2015).

They work on β -cells to preserve the secretion of insulin. As a result, it is used as a treatment plan for insulin resistant in T2DM patients, showing lasting effects for up to 5 years (DeFronzo et al., 2013). The main types of thiazolidinediones include rosiglitazone maleate and pioglitazone. Pioglitazone is contraindicated in patients with T1DM, and for the treatment of diabetic ketoacidosis (Monographs.iarc.fr., 2018).

A common side effect of TZD is increased body weight. However, the greater the weight gain, the better in HbA1c lowering as well as recovery in β -cell functions and insulin sensitivity (Gastaldelli et al., 2007). Nevertheless, these medications have associated drug-specific increased risks of fluid retention, heart failure, or bladder cancer, indicating they should be prescribed with caution and careful examination of the risk/benefit ratio (Kleinberger & Pollin, 2015).

In fact, rosiglitazone was previously banned by the FDA due to the great number of cardiovascular related events, but the ban has currently been lifted and pioglitazone is contraindicated in class III to IV cardiac failure patients. Furthermore, the clinical use of pioglitazone is further limited by the spectrum of side effects that include weight gain, decrease in hematocrit values, edema, heart failure, fractures, and worsening of diabetic macular edema (Jearath et al., 2016).

Dipeptidyl peptidase-4 (DPP4) inhibitors

The newest class of oral antidiabetic medications act through the incretin signaling pathway (Kleinberger & Pollin, 2015). These medications include DPP4 inhibitors, also called as gliptins, a group of medications which works by inhibiting the enzyme, dipeptidyl peptidase 4 (Vijan, 2015). Inhibition



of this enzyme is responsible for delaying the inactivation of incretin hormones such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are involved in regulating glucose homeostasis physiologically (Vijan, 2015) (Kleinberger & Pollin, 2015).

DPP4 inhibitors are a novel type of oral glucose-lowering agent that modulate fasting plasma glucose, postprandial glucose, and HbA1c levels by decreasing the inactivation of endogenous incretins to stimulate the release of insulin in a glucose-dependent manner. Combining insulin with a DPP4 inhibitor has been well documented to reduce HbA1c levels with less weight gain and incidence of hypoglycemia in patients with T2DM.

Several studies have indicated that DPP4 inhibitors could be used for T1DM. A study showed that there was a significant reduction in HbA1c with sitagliptin compared with placebo in patients with T1DM (Ellis et al., 2011), while other randomized control trials did not find significant differences in HbA1c levels between patients with DPP4 inhibitors and placebo (Zhao et al., 2014).

Promoting the incretin signaling induces insulin secretion, inhibits glucagon secretion, reduces gastric emptying, and decreases appetite (Kleinberger & Pollin, 2015). These drugs, such as sitagliptin, saxagliptin, alogliptin and linagliptin (Vijan, 2015), have fewer reported adverse effects than other classes of oral antidiabetic medications, low hypoglycemia risk and show weight neutrality (Tan et al., 2019).

The main types of DPP4 inhibitors include sitagliptin, saxagliptin, alogliptin, and linagliptin. Alogliptin has been generally well-tolerated and has demonstrated a reduction in HbA1c when administered alone or as add-on/combination therapy with other antidiabetic agents (Kaku et al., 2019). Linagliptin is of particular interest in the context of diabetic nephropathy as it is the only compound that is not predominantly excreted in the urine (Krentz, 2018).

However, several studies have demonstrated no significant short-term benefits of DPP-4 inhibitor for morbidity/mortality and micro-/macrovascular clinical complications in patients with T2DM. Overall, the benefit–risk balance of this group of hypoglycemic drugs does not appear to favor the prevention of clinical complications of T2DM unless proven otherwise (Rehman et al., 2017).

Glucagon-like peptide 1 (GLP-1) analogs

Another class of oral antidiabetic medication that act through the incretin signaling pathway includes GLP-1 analogs that act as incretin mimetics (Kleinberger & Pollin, 2015).

The use of GLP-1 analogs, such as albiglutide, dulaglutide, exenatide and liraglutide (Vijan, 2015), are basically as incretin-based therapies that increase the secretion of insulin via a glucose-dependent fashion, decrease the secretion of glucagon and ultimately repress the production of hepatic glucose. A lasting lowering in HbA1c of up to three years has been observed. Although these drugs are not as tolerable as DPP4 inhibitors, they bring about better lowering in HbA1c levels and stimulate weight loss. They rectify endothelial dysfunctions, prolong gastric emptying time, improve lipid profiles and lower blood pressure (Tan et al., 2019).

GLP-1 can regulate blood glucose by promoting insulin secretion from pancreatic β -cells, inhibiting



inappropriate glucagon secretion from pancreatic α -cells, delaying gastric emptying and controlling appetite. In addition, GLP-1 does not induce insulin secretion at low levels of blood glucose; therefore, it can effectively reduce both glycated hemoglobin levels and the risk of hypoglycemia (Wang et al., 2017). The main types of GLP-1 analogs include albiglutide, dulaglutide, exenatide and liraglutide.

The most frequently reported adverse effects with GLP-1 analogs are mild to moderate nausea (dose-dependent) and vomiting (Vilsbøll & Knop, 2008).

Sodium–glucose co-transporter-2 (SGLT2) inhibitors

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of prescription drugs that are approved by EMA and FDA for use in T2DM to lower blood glucose levels along with diet and exercise. They are currently not approved for use in T1DM (Fattah & Vallon, 2018). Although, previous studies (Li & Xu, 2019), (El Masri et al., 2018) also confirmed that SGLT2 inhibitors are effective when used to treat T1DM (Huang et al., 2020).

SGLT2 inhibitors, also known as gliflozins, suppress sodium transport and boost glucose elimination via the kidneys by inhibiting glucose absorption in proximal renal tubules, thus lowering the plasma blood glucose concentration. Pharmacological agents in this class include canagliflozin, dapagliflozin and empagliflozin (Vijan, 2015). They can be used in patients at any stage of diabetes because they work independently on insulin. These drugs can improve β -cell functions, enhance insulin sensitivity and ameliorate glucotoxicity as a result of glucosuria. They have the ability to decrease HbA1c levels by 0.5% to 1%, reduce weight and lower blood pressure (Tan et al., 2019).

By inhibiting SGLT2, glucosuria is increased and serum glucose levels decline, particularly in hyperglycemic patients. The effect is enhanced in the setting of hyperglycemia since the latter increases the filtered load of glucose to the proximal tubule, which enhances glucose reabsorption via SGLT2 and as a consequence the glucosuric effect of SGLT2 inhibition. This glucosuric effect may further increase due to a diabetes-associated increase in renal SGLT2 expression (Fattah & Vallon, 2018).

The main types of SGLT2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin.

However, SGLT2 inhibitors can have potential side effects, such as enhance ketogenesis or can lead to diabetic ketoacidosis and infection (Fattah & Vallon, 2018) (Huang et al., 2020).

Combination therapy

Combination therapies are started to get faster, more effective control on blood glucose and dose reductions in individual medications. It is normally initiated when monotherapy is inadequate in keeping blood glucose levels under control (Tan et al., 2019). Exogenous insulin can be combined with various oral antidiabetic drugs to allow insulin dosage lowering. Combining insulin with metformin or TZD improves glycemic control (Eng et al., 2014). When basal insulin is combined with GLP-1 receptor agonists, HbA1c levels are decreased accompanied by a reduction in weight (Eng et al., 2014). SGLT2 inhibitors are mainly applied together with either metformin. It can also be used in combination with DPP4 inhibitors to improve glycemic control and reduce weight, without raising the risk of



hypoglycemia (Tan et al., 2019).

Therapy for T1DM

Insulin is the mainstay of therapy for individuals with T1DM (American Diabetes Association, 2017). The oral anti-hyperglycemic medications approved in T2DM, may also be of benefit in T1DM, in addition to insulin, although they have not yet been approved for this indication (Fattah & Vallon, 2018).

The recent larger trials provide a new perspective on the use of metformin in T1DM (Livingstone et al., 2017). Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled T1DM (American Diabetes Association, 2017). Metformin can reduce weight and LDL-cholesterol and might reduce atherosclerosis progression, over 3 years in middle-aged people with long-duration T1DM already treated with antihypertensive agents and statins (Livingstone et al., 2017).

Combination therapy with insulin and GLP-1 can effectively improve HbA1c levels, cause weight loss and reduce the dosage of insulin. In addition, it can also reduce the risk of hypoglycemia. Several randomized controlled trials have confirmed that this treatment may be just as effective for T1DM patients (Wang et al., 2017).

SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2 (American Diabetes Association, 2017). The mechanistic effects like a reduction in glomerular hyperfiltration, blood pressure, volume overload, and body weight, as well as lowering blood glucose without increasing the hypoglycemia risk, are induced in T1DM patients treated with SGLT2 and insulin (Fattah & Vallon, 2018).

The FDA and EMA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic diabetic ketoacidosis) in patients with T1DM and T2DM treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain (American Diabetes Association, 2017).

A meta-analysis (Rehman et al., 2017) about DPP4 inhibitors in patients with T1DM showed that DPP4 inhibitors combined with insulin do not increase or decrease the risk of hypoglycemia and do not decrease HbA1c levels (Rehman et al., 2017). DPP4 inhibitors reduced daily insulin dosage significantly but did not reduce HbA1c level.

Therapy for T2DM

Lifestyle interventions and metformin constitute the initial treatment to T2DM recommended in nearly all guidelines. However, if metformin monotherapy results in an HbA1c value that is still elevated above the agreed-upon target range (generally between 6.5% and 7.5%), then the treatment can be amplified with the addition of a second antidiabetic drug (combination therapy) (Pfeiffer & Klein, 2014).

The combination of a sulfonylurea or repaglinide with metformin has a clear antihyperglycemic effect. Its disadvantages include the risk of hypoglycemia and the danger of weight gain and, possibly,



cardiovascular side effects (Pfeiffer & Klein, 2014).

Injectable GLP-1 receptor agonists have also been approved for use in combination with metformin. Their GLP-1-like effect is stronger and longer lasting than that of the DPP-4 inhibitors; aside from lowering the blood glucose level and the HbA1c fraction, the GLP-1-like effect also slows gastric emptying and stimulates the hypothalamic satiety center (Pfeiffer & Klein, 2014). Thus, GLP-1 receptor agonists tend to cause weight loss, particularly when compared to insulin or sulfonylureas. A combination of metformin with a GLP-1 receptor agonist is highly effective, confers only a low risk of hypoglycemia, and can help the patient lose weight; it is therefore especially advantageous for obese patients, for those who are prone to hypoglycemia, and for those who, for occupational reasons, must keep their risk of hypoglycemic episodes to a minimum. If metformin is contraindicated, a GLP-1 receptor agonist can be combined with a sulfonylurea although hypoglycemia may arise with this combination (Pfeiffer & Klein, 2014).

The DPP-4 inhibitors have a broader therapeutic application and a low risk of causing hypoglycemia when they are given as monotherapy or in combination with other drugs that only rarely cause hypoglycemia (Pfeiffer & Klein, 2014).

Basal insulin is often given in combination with an oral antidiabetic drug. As long as metformin is not contraindicated or poorly tolerated, metformin can continue to be given when insulin therapy is started, and over the further course of insulin therapy as well (Pfeiffer & Klein, 2014). This lowers overall insulin consumption and also causes less weight gain than insulin treatment alone. It remains unclear whether any additional benefit can be gained from supplementing basal insulin therapy (with or without metformin) with another drug to increase postprandial insulin secretion, e.g., a sulfonylurea, GLP-1 receptor agonist or DPP-4 inhibitor (Pfeiffer & Klein, 2014).

LIFESTYLE

Diabetes management should target lifestyle modifications, including dietary and physical activity interventions, in addition to the use of pharmacological treatment when necessary. In the case of T2DM, being a disease directly related to adverse lifestyles, the main focus for effective management should be lifestyle interventions. With respect to T1DM, despite being treated primarily with insulin, it is necessary to consider dietary and physical activity modifications to optimize results, also due to the proportion of people with T1DM who are obese and therefore increase their insulin needs and adversely affect their metabolic control (Mottalib et al., 2017). Lifestyle changes, mainly diet and exercise, have shown benefits in the management of T2DM and T1DM, as well as in future complications related to the disease (Raveendran et al., 2018).

Dietary interventions and medical nutrition therapy

T2DM

Nutritional interventions are important in achieving optimal glycemic control in patients with T2DM (Raveendran et al., 2018). The results of the Look AHEAD trial have demonstrated that intense lifestyle interventions are associated with improved glycemic control (Dutton & Lewis, 2015). Also, different recent studies have proven the association between diet quality and mortality, being evaluated the



quality of the diets based on the Healthy Eating Index (HEI), the Alternate Healthy Eating Index (AHEI), and the Dietary Approaches to Stop Hypertension (DASH). The results obtained show that high-quality diets are associated with a significant 22% reduction in mortality in patients with T2DM (Schwingshackl et al., 2018). According to another systematic review, compared to individuals with the least healthy lifestyle, those with the healthiest lifestyle have a 56% lower risk of all-cause mortality, 49% lower risk of cardiovascular disease mortality, 31% lower risk of cancer mortality, and 52% lower risk of incident cardiovascular diseases (Zhang et al., 2020).

The term medical nutrition therapy (MNT) is used by The American Diabetes Association (ADA) to define the optimal combination between dietary intake and diabetic therapy (pharmacological and non-pharmacological) in order to achieve a better prognosis (Bantle et al., 2006). In the case of patients diagnosed with T2DM, MNT can be used as a secondary prevention measure, aiming at tighter glycaemic control and reducing diabetic complications (Bantle et al., 2006), and as a tertiary prevention measure to manage diabetes-related complications. Glycemic control can be improved with low-glycemic index diets, which reduce postprandial blood glucose excursions, as well as with low-calorie diets, diets with non-nutritive sweeteners, or by increasing daily fiber intake. Similarly, hypocaloric and low carbohydrate diets help control weight along with metabolic control of T2DM (Raveendran et al., 2018).

Diabetes-specific formulae adopted in MNT have resulted in a significant reduction of glycated hemoglobin (HbA1c) levels, postprandial glucose levels and insulinemic responses in diabetes (Goodpaster et al., 2010). MNT with low-carbohydrate, low-glycemic index, and high-protein diets or with a Mediterranean diet significantly improved glycemic control in patients with T2DM, according to a meta-analysis including 16 studies of at least 6 months duration (Ojo & Brooke, 2014). Specifically, the Mediterranean diet has been associated with the greatest reduction in HbA1c (-0.47%) and body weight (-1.84 kg on average). In patients with T2DM, in addition to being beneficial in glycemic control, the Mediterranean diet reduces insulin resistance and the risk of cardiovascular factors. Patient adherence, acceptability and long-term management are key aspects of the effectiveness of the diet as a treatment. This is another reason why the Mediterranean diet is more successful and realistic for patients with T2DM, as it is a moderate diet that includes all food groups, making it more likely that patients will maintain it in the long term (Chester et al., 2019).

T1DM

The principles of MNT are also applicable to the management of T1DM, considering that doses of insulin should be calculated on the basis of carbohydrate counting. According to a recent meta-analysis, better and significant reductions in HbA1c have been achieved with this strategy (Fu et al., 2016). The carbohydrate counting approach is also beneficial for patients at risk of hypoglycemia (Gillespie et al., 1998).

Physical activity

T2DM

Physical activity improves glycemic control, insulin sensitivity, bodyweight, cardiovascular risk factors, physical fitness, lipid level, blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein and overall wellbeing, reducing at the same time the risk of cardiovascular morbidity and



mortality in patients with T2DM. (Froberg & Andersen, 2005), (Reiner et al., 2013).

Patients with T2DM should be pre-screened by health care providers before starting a physical activity program, especially in individuals with a sedentary lifestyle. On the other hand, exercise increases the risk of hypoglycemia in T2DM, especially in patients taking insulin/insulin secretagogues, so the dose should be preadjusted by professionals. The risk of hypoglycemia varies according to the duration and intensity of exercise, as well as the time since the last meal. Increased insulin sensitivity caused by exercise can result in hypoglycemia several hours after exercise (Qaseem et al., 2012), (American Diabetes Association, 2012).

The improvement in sensitivity to insulin produced by exercise lasts between 24 and 72 hours, and in the case of patients with T2DM they must perform regular exercise with no more than 2 consecutive days without physical activity to maintain the benefits (Burchfiel et al., 1995).

T1DM

A recent systematic review has shown that exercise training for resistance, endurance and a combination of both improves glycemic control and diabetes outcomes in patients with T1DM (Röhling et al., 2016). However, there is also a risk of hypoglycemia during and after exercise, as well as possible post-training hyperglycemia because of counter-regulatory hormones. Therefore, insulin treatment may need to be modified in patients who do only occasional unaccustomed physical activities. The benefits of exercise depend on factors such as frequency, duration, intensity, type of exercise, age of the patient and the adherence to the exercise program. Changes in blood glucose patterns with exercise depend on the type of exercise; mild-to-moderate aerobic exercise decreases glucose levels, while intense aerobic and anaerobic exercise and exercises with a load-profile stabilize or increase glucose levels (García-García, 2015). For continuous physical activity at moderate intensities, glycemia declines rapidly, while recoveries immediately afterwards are gradual. For resistance activity (e.g. weightlifting) more constrained decays are observed (García-García, 2015).

MEDICAL DEVICES TO IMPROVE DIABETES TREATMENT

Medical devices for insulin therapy

Pharmacologic research in diabetes has explored a multitude of options for delivering insulin including the use of injections, Continuous Subcutaneous Insulin Infusion (CSII) or insulin pump therapy, and, more recently, the ability to integrate inhaled insulin therapy into the daily injectable insulin regimen (Odegard & Capoccia, 2007). Insulin can be administered subcutaneously via various methods such as vial and syringe, insulin pen continuous subcutaneous insulin infusion (CSII) systems, and transcutaneously via jet injectors (Shah et al., 2016).

Currently, two modes of insulin delivery for diabetic patients are widely used. The first is based on multiple daily injections (MDI), which involves several shots of short-acting prandial insulin, along with 1-2 doses of a long-acting basal preparation. The second route is CSII, which provides a constant supply of insulin via an insulin pump with superimposed meal-related boluses (Rys et al., 2018). Both technologies have evolved with the development of insulin preparations and analogs with favorable pharmacodynamic characteristics and of sophisticated insulin pumps with better safety and usability



profiles (Fatourechi et al., 2009). However, in the general T1DM population, it has been shown that when compared with MDI, CSII was associated with a slightly lower HbA1c level and a smaller risk of severe hypoglycemia (Rys et al., 2018).

Insulin syringes

Insulin syringes are characterized by three factors, i.e. needle gauge, needle length and syringe capacity. The manufacturers of the syringes offer a wide array of sizes and styles. Almost all syringes available today are disposable and come with microfine needles. The proper selection of an appropriate syringe is based on several considerations, like chemical composition of the material from which syringes are made, syringe capacity, ease with which air bubbles are removed, clarity of the markings on the syringe barrel and convenience of syringe disposal. In addition, one must consider the condition of the patient with respect to his/her ability to operate the syringe safely and effectively (Al-Tabakha & Arida, 2008).

While conventional syringes offer a wide choice of products that are easy to read and operate, the disadvantages include their bulky construction and the required time and practice to learn optimal syringe technique. Furthermore, the required syringe manipulations in the social setting (such as workplace, classroom and public places including department stores, playgrounds and restaurants) may be considered as drawbacks. In some cases, patients need to mix different types of insulin preparations in one syringe to meet their individual needs, which can be cumbersome and complicated. In patients with less dexterity, this may result in inaccurate doses, compromising their glycemic control (Al-Tabakha & Arida, 2008).

Insulin pens

Pen devices are novel in that they combine the insulin container and the syringe into a single modular unit. Insulin pens eliminate the inconvenience of carrying insulin and syringes. Many pens are available in a variety of types and shapes. There are two main types of pens, reusable or a prefilled device. In the former case, the patient must load an insulin cartridge prior to use. Regardless of the type, both pens hold cartridges containing insulin. The number of steps required to change an insulin cartridge with reusable pens varies between the different pen devices. Prefilled devices are well accepted in a bedtime insulin regimen for T2DM patients (Al-Tabakha & Arida, 2008).

Reusable insulin pens offer a wide range of advantages such as their durability, eliminating the need of cartridge refrigeration and flexibility in carrying three to five-day supplies. The pens also offer discreetness by resembling a fountain pen. The refilled insulin pens are smaller in size and lighter in weight. They cause minimal pain due to the finest and shortest disposable insulin needles. In addition, they are quick and easy to use as they resemble the fountain pen (Al-Tabakha & Arida, 2008).

The major disadvantage of using insulin pens, like other new diabetes technology, are the costs. Insulin analogs are ~ 30% more expensive per unit when purchased as prefilled or refillable pens than when purchased in vials (Fowler, 2008).

Continuous Subcutaneous Insulin Infusion (CSII) systems

Treatment with Continuous Subcutaneous Insulin Infusion (CSII) is currently the most physiological



way to replace both the basal component of insulin secretion, as it can be adjusted to the different physiological requirements existing throughout the day, as well as to the endogenous insulin secretion elevations associated to meal intakes or insulin in response to food that is achieved by giving boluses before each intake. This type of treatment consists of the continuous administration of insulin 24 hours a day, also including rapid insulin supplements before meals.

Infusion pumps are medical devices that allow continuous insulin infusion in subcutaneous tissue. Infusion pumps contain a cartridge or a syringe full filled with short-acting insulin. The syringe/cartridge is connected to the subcutaneous tissue through an infusion set made by a plastic catheter and either a small needle or soft plastic cannula, usually placed on the abdomen. The needle or cannula should be changed every 3 days. The insulin pump releases insulin with two modalities: continuous (basal infusion) and on request (insulin boluses) (Maltoni et al., 2014).

Insulin pump therapy offers several advantages over multiple daily injection therapy. Insulin pumps are able to more precisely dose insulin compared to insulin syringes or pens (Fowler, 2008), provide accuracy and greater flexibility in insulin delivery for patients according to their individual requirements. The main disadvantage of the therapy with insulin pump is that it is very expensive as compared to the use of traditional syringes and vials (Al-Tabakha & Arida, 2008).

Insulin jet injectors

Jet injectors are devices designed to deliver a fine current of insulin flowing steadily transcutaneously at high speed and high pressure to penetrate the skin without a needle. The use of force on a fluid under considerable pressure through a very small opening allows such systems to deliver insulin without using a needle to pierce the skin. The dose is controlled by a dial-a-dose operation through a single component design in comparison to the conventional multicomponent syringe and vial method. The available jet injectors allow a dose range of 2 to 50 units of insulin and can deliver insulin in half-unit increments. Insulin that is administered by the jet injector method is absorbed rapidly without the risk of subcutaneous infection (Al-Tabakha & Arida, 2008).

The size and the cost of these jet injectors are considered unfavorably and often limit their routine use in patients with diabetes. The potential for a decreased amount of absorbed insulin over repeated administration with jet injectors is a disadvantage. Additional concerns with jet injectors include pain or bruising at the administration site and the noise the injector makes upon delivery. Pressure may be difficult to adjust and the frequency of side effects seems to be significantly higher for young children. However, jet injectors may be considered for patients suffering from needle phobia and for patients who suffer from severe lipomas (Al-Tabakha & Arida, 2008).

Insulin inhalers

The lungs, on account of their large surface area, are an ideal target for drug delivery and inhaled insulin represents one of the most promising alternatives to injection. Clinical experience has shown that inhaled insulin has the potential to be an effective treatment in patients with diabetes, with particular utility in the treatment of postprandial hyperglycemia (Al-Tabakha & Arida, 2008).

Insulin inhalers work much like asthma inhalers. The products fall into two main groups: the dry powder formulations and solution, which are delivered through different patented inhaler systems



(Al-Tabakha & Arida, 2008). Of the inhaled insulin products that have reached clinical trials, two products, both dry powder inhaler (DPI) systems, have secured FDA approval; one being Exubera[®], which also has EMA approval in Europe, and Afrezza[®] (Easa et al., 2019). Another inhaled insulin product is the pocket-sized insulin inhaler device Dance-501, which uses a vibrating mesh micropump technology developed by Aerogen.

Exubera[®], containing rapid-acting insulin in powder form (Al-Tabakha & Arida, 2008), was unsuccessful mainly because of the design of the device did not take the perspective of patients into consideration. Although theoretically envisioned well for its purpose, in practice, the device was large and bulky and, thus, difficult for patients to carry around and could not be used with discretion. Other factors that contributed to the failure of Exubera included the training required to use the device, the high cost of the product, difficult dosing equivalence, the requirement for patients to regularly check their lung function, and safety concerns over chronic use of the product (Easa et al., 2019).

The advantages of the Dance-501 are that it is small, discrete, portable, and battery operated and, hence, the developers have overcome the disadvantages faced by Exubera. Additionally, because the formulation is a liquid aerosol system, the incidence of coughs is lower compared with DPI systems, and the price of using this device is said to be comparative to that of current pen devices.

One possible drawback of the design is that the insulin release is breath actuated, which, without good initial training, could result in fluctuating bioavailability, similar to current problems faced with similar inhaler devices used for respiratory diseases. Another weakness is that, before administration, precise volumes of the formulation from a separate container are required to be dispensed into the inhaler reservoir, which adds another step to the administration process. The manual work required for the process could be a problem for older patients or those with arthritis (Easa et al., 2019).

Inhaled regular insulin is more rapidly absorbed than insulin from subcutaneous injection. However, the efficiency of inhaled insulin is lower than that of subcutaneous injection because pulmonary delivery of insulin involves that not everything is inhaled and some residue remains in the inhaler (Al-Tabakha & Arida, 2008).

Glucose monitoring systems

Home glucose monitoring allows patients and healthcare professionals to assess glucose control longitudinally and can provide real-time feedback on the effect of glucose treatments. Home monitoring is considered part of the standard of care for persons receiving insulin therapy to allow sensible dose adjustments and to help determine whether symptoms are due to hyperglycemia or hypoglycemia. The optimum frequency of home monitoring has not been formally evaluated and is usually left to the discretion of the patient and provider. The role of home glucose monitoring in guiding oral therapy is less clear; a systematic review found a small reduction in HbA1c levels at 6 months, but this benefit subsided by 12 months, suggesting that self-monitoring has no sustained effect (Vijan, 2015).

Glucose monitoring systems (GMS) are devices which provide information about glucose values ensuring an efficient and safe glucose control by detecting fluctuations in glucose levels and giving a



precise picture of the patient's condition. These devices are crucial especially for patients with high risk of hypo- or hyperglycemia (van Steen et al., 2017) (Aberer et al., 2017). Glucose monitoring has been proven to be effective in patients with T1DM. In the case of patients with T2DM, it has been associated with improved glycemic control when performed on a daily basis (Fowler, 2008). GMS constitute an alternative for regular control of glucose levels in patients with T1DM or T2DM in order to improve therapeutic outcomes or to identify and modify inappropriate patient behaviors in a timely manner. On the basis of the literature, currently available different types of GMS could be classified in several groups:

Self-monitoring Blood Glucose (SMBG)

SMBG has allowed patients much more accurate measurement of glycemic control, which in turn allows more intelligent titration of medication.

It is recommended that SMBG be performed three or more times daily for patients who follow an intensive insulin treatment either with multiple daily doses or insulin pump therapy. For patients who are on other regimens, such as oral agents, or basal insulin therapy, SMBG may still be useful to achieve adequate glycemic control, especially postprandial (Fowler, 2008).

This self-analysis is defined as the real-time self-measurement of capillary blood glucose by the patient using an accurate device, digital or battery-operated. The aim of SMBG is to collect detailed information on glucose levels at many time points during the day in order to implement various strategies to fit the patient's lifestyle. It can be used to guide a new diet, and to help people adjust their daily food intake, physical activity, and insulin dosage to improve glycemic control (Ruiz Gracia et al., 2014).

The main benefits of SMBG devices are (Ruiz Gracia et al., 2014):

- The patient does not require help and it can be performed anywhere.
- It provides immediate accurate data, which can help patients and their relatives in the daily management of diabetes.
- It informs patients whether their treatment is working and guides the health care team on whether to continue with the same treatment regimen or if another treatment is needed.
- It improves recognition of either severe hyperglycemia or hypoglycemia.
- It is important for the performance of hazardous tasks which could be influenced by high or low glycemic levels, such as driving or operating machinery.

However, the main limitation is that a single system of SMBG does not meet the needs of all people with T2DM, thus it must be adapted according to different patients' characteristics. Another negative aspect to bear in mind is the pain derived from finger prick and the cost of testing supplies (Ruiz Gracia et al., 2014).

Continuous Glucose Monitoring (CGM)

These are devices that perform frequent glycemic level measurements, allowing to quickly obtain the glucose profile of a diabetic patient (Maltoni et al., 2014). These devices consist of a subcutaneous



monitor that measures the glucose concentration of subcutaneous interstitial fluid (ISF) (usually a close approximation of blood glucose concentration) (Fowler, 2008) (Petus & Edelman, 2017). Particular attention should be given to the time span required by the glucose to pass from blood to tissues, as it represents the lag-time in variations between hematic and tissular glucose levels. This lag-time is particularly important during rapid variations of glycaemia (Maltoni et al., 2014).

CGM devices are made of (Maltoni et al., 2014):

- A small monitor (similar to a beeper) that reads and shows glucose levels in real-time or retrospectively.
- A glucose sensor, inserted in the subcutaneous tissue of the abdomen, wrist or arm.
- A transmitter sending to the monitor the data on glucose concentrations read by the sensor (by means of a wire or through a wireless technology).

A type of a CGM device is Real-Time CGM (rt-CGM) which displays continuous information about the current glucose level and glucose trends and provides the user with rate of change (ROC) arrows, which indicate the direction and velocity of changing glucose. Moreover, rt-CGM devices can program alerts that warn the user when glucose levels increase or decrease beyond a defined glycemic threshold, individualized for each patient (Petus & Edelman, 2017).

The main benefits of CGM devices are (Burge et al., 2008):

- Minimize extreme blood glucose.
- Immediate feedback impact of food, exercise or stress on blood glucose.
- Knowing the direction in which blood glucose is trending.
- Adds meaning to fingersticks.
- Reduce HbA1c.
- Identify patterns.
- Test and fine-tune basal and ISF.
- Improve hypoglycemia unawareness.

However, a relevant weakness of this type of devices is the accuracy of the measurement, since the sensor is subject to deterioration that leads to systematic measurement errors (Maltoni et al., 2014). They cause discomfort to patients, require more frequent calibration by fingerstick tests and cannot be used for more than a few days (Vashist, 2013). Furthermore, the main limitation is their high cost, which is beyond the reach of most patients (Fowler, 2008) (Vashist, 2013).

Flash Glucose Monitoring (FGM)

Flash glucose monitoring (FGM) by FreeStyle Libre (Abbott Diabetes Care Inc.) is a glucose monitoring system to continuously monitor interstitial glucose levels for up to 14 days. What is noteworthy about this system is that self-monitoring of blood glucose is not required during the 14 -day wearing period. Moreover, the accuracy of interstitial glucose measurements and the usefulness and safety of FGM has been shown (Sato et al., 2019).



The use of the FGM system resulted in significant reductions in hypoglycemia, increased time in target range, reduced glycemic variability, and greater patient satisfaction compared with self-monitoring of blood glucose (Kudva et al., 2018).

The FGM systems use two components: a disposable sensor that is inserted into the user's upper arm and a separate handheld touchscreen reader device used to scan and retrieve CGM glucose readings (Kudva et al., 2018).

When the reader is swiped close to the sensor, the sensor glucose data are transmitted to the reader. The reader displays the current glucose concentration and the most recent 8 hours of sensor glucose readings, as well as trend arrow data when present. When >8 hours occur between scans, only the last 8 hours of data are reported. Importantly, the system lacks automatic alarms. Therefore, patients must be actively engaged in scanning because they will not receive automatic alarms in the event of hypoglycemia or hyperglycemia, as is the case with other CGM systems (Kudva et al., 2018). The system measures glucose concentrations every minute and, when scanned, transmits the current glucose reading and historical glucose readings in 15-minute increments to the reader (Bidonde et al., 2017).

A type of FGM device is Intermittent scanned continuous glucose monitoring (isCGM) which has the ability to allow for greater personalization of diabetes self-management, a less painful and more convenient method for glucose monitoring and may allow for a more comprehensive assessment of glycemia with potential for improved adherence (Cowart et al., 2020).

A notable difference between real-time (rtCGM) and isCGM is that isCGM devices do not have an alarm feature, and do not communicate with the user continuously through connectivity with continuous subcutaneous insulin infusion (CSII) devices, only on demand, or "intermittently". Similar to rt-CGM, the isCGM device measures interstitial glucose (Cowart et al., 2020).

The advantage of the FGM is the continuous provision of information about interstitial glucose concentration that can facilitate adjusting insulin dosage. The technology is factory calibrated, which means that the individual does not have to perform daily SMBG by finger prick, the sensor is small and can easily be hidden under clothing, and it is water resistant (Bidonde et al., 2017). Moreover, it has the ability to assess glycemic measures and has been associated with high patient satisfaction and lower diabetes distress with FGM use as compared with usual care (Cowart et al., 2020).

Disadvantages of FGM are potential skin irritation, and associated costs (the sensor has to be replaced every 14 days); there can be some delay in the measurement, which may impede optimal monitoring. Unlike other real time continuous glucose monitors, FGM does not have an alarm, and it does not work in synchronization with an insulin pump (Bidonde et al., 2017).

CONCLUSIONS

Type 1 and Type 2 Diabetes need to be managed in a long-term basis by clinicians following different sequences of treatment, mainly pharmacological, but also considering lifestyle, educational factors



and technological approaches based on medical devices.

Pharmacologic treatment for diabetes facilitates excellent control, being injected insulin and oral antihyperglycemic agents as the main alternatives. Consideration of individual characteristics and existing comorbidities help to choose the most appropriate drugs for therapy adjustments, optimizing treatment and preventing disease progression and complications. Combination therapy is usually started for faster, more effective glycemic control and dose reductions in individual medications. It is normally initiated when monotherapy is inadequate in keeping blood glucose levels under control.

The main advances in medical devices for the last decades have contributed to improve glycemic control. For intensive insulin treatment regimens, continuous subcutaneous insulin infusion systems are associated with better outcomes in T1DM. Glucose monitoring devices such as continuous glucose monitoring and Flash glucose monitoring help to detect fluctuations in glucose levels along the day and give a precise picture of the patient's condition, improving the patient's self-management and thus glycemic control.



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