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Abstract

The diabetes pandemic demands solutions for proper glycemic control and prevention of future chronic complications that could result in organ failure or comorbidities. In this regard, we now know that patients diagnosed with diabetes require individual management plans. Thus, new treatment management strategies have been designed to allow clinicians to tailor the most appropriate therapy for diabetes patients individually. These treatment management plans extend beyond defining the appropriate medications for patients; they provide a directive toward some acute and chronic complications that should be screened for, as they are historically known to occur with diabetes. Observing any of the complications or comorbidities required the patient medication regimen to be adapted accordingly. This chapter describes such modern treatment plans for the two primary forms of diabetes, type 1 and type 2, based on both basic and clinical studies, later incorporated in various diabetes management guidelines and outlines expected future trends.

Keywords: diabetes; delivery of insulin; islet transplantation; stem cells therapy; hyperbaric oxygen therapy; pharmacotherapy of diabetes.

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1. Introduction

Diabetes mellitus (DM) is an endocrine disease, characterized by hyperglycaemia and multiple metabolic disorder that causes serious local and systemic (Nair 2007; Forbes, Cooper 2013; Katsarou et al. 2017). Nowadays, DM is one of the biggest health problems that has reached pandemic proportions (Forouhi and Wareham 2014). According to the International Diabetes Federation, 425 million people worldwide have DM, with a tendency to be 629 million in 2045 (Cho et al. 2018). There are at least five types of DM, while the two primary forms are DM type 1 (DMT1) and DM type 2 (DMT2) (ADA 2010; Katsarou et al. 2017; Cho et al. 2018). Autoimmunity is a significant factor in the development of DMT1, while genetic predisposition and obesity are leading risk factors for the development of DMT2 (Al-Goblan et al. 2014; Nair 2007). Despite these worrying facts, all types of DM are treatable.

The long-term anti-diabetic pharmacotherapy and lifestyle adaptations are necessary to achieve glycemic control and decline multisystem disorders in DM patients (Rai et al. 2016; Katsarou et al. 2017). Nearly one century ago, exogenous insulin became available, and since that, there is constant progress in designing new and more sensitive treatment options (Banting, Best 1990; Maclean 1926). In the meantime, plenty of oral hypoglycaemics are designed, and they achieve desirable results in patients with DMT2 (Butterfield et al. 1957; Krall et al. 1958). However, the exogenous insulin is irreplaceable in the treatment of people with DMT1 and required in abundant cases of DMT2 (Handelsman et al. 2015). Despite constant progress in terms of the new therapeutic approaches, a comprehensive and efficacious cure for DM is still not realized. The current therapies for patients with DM have several shortfalls, including the efficacy

of the therapies, knowledge of timings between administration of therapies, and inadequate glycaemic control (Shah et al. 2016; Castle et al. 2017; Evans et al. 2011; Pathak et al. 2019). Also, these therapies produce numerous side effects like gastric irritation, injection phobia, diarrhea, loss of appetite, and others (Pathak et al. 2019; Rai et al. 2016; Zaric et al. 2019).

This chapter summarized the current trends and future perspectives in the treatment DM.

2. Aetiology and pathophysiology of DMT1 and DMT2

Diabetes mellitus (DM) is a carbohydrate metabolism disorder characterized by alterations and impairment in insulin secretion and/or action that leads to hyperglycaemia (Ergun-Longmire and Maclaren 2000; ADA 2009; Lebovitz 1984). Besides the increased blood glucose level, DM is also characterized by other biochemical disorders arising as a consequence of inadequate regulation of insulin synthesis/ actions which all together contribute to progression of the disease and its association with long-term injury, dysfunction, and failure of different organs, especially the blood vessels and heart (Jovanovic et al. 2017; Obradovic et al. 2017; Sudar Milovanovic et al. 2015; Sudar-Milovanovic et al. 2017; Obradovic et al. 2015; Soskic et al. 2011) but also the nerves, kidneys, and eyes (ADA 2009). Study results obtained in the field of genetics, epidemiology, etiology, and pathophysiology of DM states, showed that diabetes is not a single disease, but preferably a clinical disorder with a set of various medical signs and symptom and primarily identified by an improper increase of fasting and/or postprandial serum/plasma glucose level accompanied by the development and spreading of long-term micro- and macro-vascular, as well as neuropathic alterations (Lebovitz 1984).

The overall prevalence of DM among adults over 18 years of age is steadily growing, and it has been increasing more rapidly in countries with low- and middle-income economies. The growth in DM prevalence reflects the rise in its leading risk factors; overweight and obesity, which is a consequence of physical inactivity and unhealthy diets (Roglic 2016). The World Health Organization (WHO) database and statistics show DM prevalence grew from 4.7% (1980) to 8.5% (2014), and WHO estimated that diabetes was the seventh leading cause of death worldwide in 2016 (WHO). Furthermore, DM is in the range of the most common causes of death concerning that diabetes is one of the leading causes of stroke, heart and kidney failure, blindness, as well as lower limb amputation.

There are two main categories, DMT1 and DMT2, related to the etiopathogenesis of diabetes (ADA 2009). DMT1 or juvenile diabetes is a multifactorial autoimmune disease that develops under the influence of environmental or/and genetic factors (Atkinson et al. 2014; Ikegami et al. 2011). DMT1 mostly develops in patients at a young age, before the age of 30. The most common signs and manifestations of DMT1 are weight loss, polyuria, polydipsia, and polyphagia; it develops typically in lean subjects and usually appears as ketoacidosis. The main characteristic of DMT1 is a complete lack of insulin production, and DMT1 patients are dependent on exogenous insulin application. Alterations of the pancreatic islets/beta cells structure and function, present in DMT1, mostly lead to absolute failure in insulin secretion.

DMT1 is an immune-mediated type of DM, and typically an autoimmune demolition of the insulin-secreting beta cells is basis on DMT1 development. Factors involved in its pathogenesis trigger lymphocyte infiltration in pancreatic beta cells, and the consequent

production of different proinflammatory cytokines responsible for the pancreatic beta cells destruction (Fatima et al. 2016).

Increased risk for DMT1 is generally recognized in patients by serological confirmation of an autoimmune process occurring in pancreatic islets/beta cells, considering that this is one of the first pathological alterations in DMT1 patients' pancreas and additionally by genetic markers determination (ADA 2009). At the time of DMT1 diagnosis, in 80 to 85% of patients, anti-islet antibodies are detected in the serum (Lebovitz 1984). Also, some patients with DMT1 and without registered beta cell autoimmunity have no underlying defects in insulin secretion, but their inherited defects generally cause their illness development in pancreatic beta-cell sensitivity for glucose (Ergun-Longmire and Maclaren 2000). DMT1 is genetically different from other types of diabetes, and beyond the autoimmune destruction of beta cells, there are toxic as well as viral destructions of beta cells as well (Lebovitz 1984). Linked to the genetic basis for DMT1 development are the human leukocyte antigen (HLA) genes. Moreover, there is a strong correlation between DMT1 and other endocrine autoimmunity.

Another etiopathogenetic form of DM is a non-insulin-dependent DMT2, which is a much more prevalent category and represents the vast majority (85 - 90%) of DM cases. DMT2 is a heterogeneous, progressive metabolic and endocrine illness, and it occurs as an interplay of various genetic as well as numerous environmental factors. The underlying origin of DMT2 development is the different degrees of insulin resistance in combination with deficient compensatory beta-cell reaction and adequate insulin secretion (ADA 2009). The impairment of insulin-secreting pancreatic beta cells functions notably shows progression over time.

Substantial risk factors for the development of resistance to insulin action and, consequently, DMT2 are overweight and obesity. In general, DMT2 and diabetic ketoacidosis do not appear together, and although insulin therapy may sometimes be required to optimise fasting blood glucose level, therapy with insulin is not regularly required to maintain necessary life functions (Lebovitz 1984). The genetics of DMT2 and DMT1 are distinct. DMT2 is not firmly associated with HLA antigen, and also serum antibodies against islet cells are generally absent, but there is an apparent familial connection in DMT2 patients (Lebovitz 1984). Also, a reduction in the pancreatic islets of beta cells and their function is typical, but they are usually present in a sufficient amount.

When DMT2 patients with normal ranging fasting plasma glucose but with postprandial hyperglycaemia, exhibits impaired insulin action, usually it is caused by a reduction of total insulin receptor number (Belfiore et al. 2009; Obradovic et al. 2019), while in DMT2 patients with fasting hyperglycaemia, the defects of insulin action are generally caused by aberrations in post-receptor insulin signaling (Lebovitz 1984).

3. Treatment options for DM

3.1. Delivery of insulin, islet transplantation, and stem cells

The management of DM has proposed to recover glycaemic control and reduced micro- and macro-vascular complications by administrating pharmacological therapy and modifications of lifestyle (Expert Committee of the Canadian Diabetes Advisory Board 1992; Pathak et al. 2019). Currently, insulin replacement therapy represents the first-line option for the treatment of insulin-dependent DM patients (Pathak et al. 2019). However,

one of the significant challenges in the treatment of patients with DM is the efficacy of exogenous insulin in achieving long term normal ranging glycaemia (Yeh et al. 2012). Evidence from the literature suggests a better solution for maintaining normoglycaemia than multiple daily injections, is the use of continuous insulin infusion pumps (Yeh et al. 2012; Heller et al. 2017; 2017). Also, the creation of insulin analogs with different times of action, from rapid and short-acting to ultra-long acting, contributed to improvements in therapy (Shah et al. 2016; Pathak et al. 2019). Implementation of these technological advances does not prevent the long term insulin independence, and adverse effects like invasiveness (Shah et al. 2016). To avoid such complications, researchers proposed new routes for insulin administration beyond the standard subcutaneous route (Rys et al. 2018; Atkinson et al. 2014), such as ocular (Chiou et al. 1989; Xuan et al. 2005), nasal (Kullmann et al. 2018; Benedict et al. 2007; Schopf et al. 2015; Schmid et al. 2018), buccal (Campisi et al. 2010; Caon et al. 2015), oral (Krauland et al. 2004; Fonte et al. 2013), pulmonary (Mastrandrea 2010; Ledet et al. 2015), vaginal (Vermani and Garg 2000; Ning et al. 2005), rectal (Yun et al. 1999; Yamasaki et al. 1981), and transdermal delivery systems (Zaric et al. 2019; Bariya et al. 2012).

Developed drug delivery carrier systems protect antidiabetic drugs from enzymatic degradation at the absorption site and ensure their delivery at the optimal and effective concentration for a more extended period at the target site (Rai et al. 2016). The encapsulation of insulin in particles increases its potential and allows its appropriate transport to the specific site to better control of DM (Rai et al. 2016; Zaric et al. 2019). These particles are usually micro-sized or nano-sized. The microparticle system adjusts the pattern of drug release and improves the hypoglycemic effect of oral delivery of insulin

(Wong et al. 2018). Furtado *et al.* (Furtado et al. 2008) have synthesized poly(fumaric-co-sebacic) anhydride microspheres for oral insulin delivery that successfully maintain normoglycaemia for 15 h. Despite all benefits, the main limiting factors of microparticle systems are the size of particles and the hydrophilic/hydrophobic nature that makes difficult their transport through biological membranes (Wong et al. 2018). The use of nanocarriers as a potential vehicle of insulin reduces these obstacles (Bahman et al. 2019). The small size and structural diversity of nanoparticles increase the potential of insulin through better absorption and distribution, site specificity and protection from enzymatic degradation (Bahman et al. 2019). Also, this form of application extends the release pattern of insulin and decreases the frequency of dosage, facilitating normoglycaemia for a more extended period, up to 22 days (Peng et al. 2012). Other approaches considered for delivery of insulin and antidiabetics include encapsulation in liposomes, vesicular systems made of a lipid bilayer (Huang, Wang 2006; Karathanasis et al. 2006), non-ionic surfactant vesicles called niosomes (Pardakhty et al. 2007; Ghanbarzadeh et al. 2015), and electroporation delivery of insulin within polymer vesicles over the skin (Rastogi et al. 2010).

The use of continuous insulin infusion pumps and glucose monitoring has enabled a constant movement towards artificial pancreas development (Boughton and Hovorka 2019). Pancreas or islets transplantation seems to be the best choice to prevent dependence on insulin, but donor shortages limit this option. Although islet transplantation has substantially enhanced in the past 2 decades, there are still limitations like instant blood-mediated inflammatory reaction, ischemia-induced loss of islet, harmful effects of immunosuppressive drugs, and apoptosis of transplanted cells (Bottino

et al. 2018; Johansson et al. 2005; Bennet et al. 2000). The first xenotransplantation of pig-derived islets to human DMT1 patients, in 1994, exhibited poor effects on circulating glucose concentrations (Groth et al. 1994). After this attempt, several clinical studies have described the beneficial result of using pig-derived islets for the DMT1 patient's treatment (Wynyard et al. 2014; Semaan et al. 2013). Some progress has been made using genetically modified xeno-islets to overexpress anti-apoptotic gene *B-cell lymphoma 2* (Contreras et al. 2004). Also, the technique of islets encapsulation was developed to eliminate immune-rejection of transplant and to increase islet survival and function (Korsgren 2017; Pellegrini et al. 2016; Schaffellner et al. 2005). However, the increased risk of porcine endogenous retrovirus activation, and decreased insulin production due to encapsulation, limited this procedure (Semaan et al. 2013).

Literature evidence suggests that stem cells generating new beta cells represents a promising approach for long-term treatment of DM (Stanekzai et al. 2012; Cierpka-Kmiec et al. 2019; Aguayo-Mazzucato, Bonner-Weir 2010). Many studies show that human embryonic stem cells can be used for beta cells generation and transplantation in patients with DMT1 (Pagliuca and Melton 2013; Cierpka-Kmiec et al. 2019; Kalra et al. 2018). However, clinical implementation of this treatment option has some difficulties regarding the generation of genetically stable cells, the survival rate of the cell, the potential of transplanted cells, and ethical issues considering utilization of embryo-derived stem cells (Kalra et al. 2018; van der Windt et al. 2007). Some of these issues are overcome using induced pluripotent stem cells generated from somatic cells of patients with DMT1 to produced functional beta cells (Kalra et al. 2018; Kunisada et al. 2012). Transplantation of insulin-producing human embryonic stem cells into streptozotocin-

induced diabetic mice resulted in long-term normalization of blood glucose levels (Vegas et al. 2016). Studies also demonstrate beta cell neogenesis initiated from different adult stem/progenitor cells (Jun and Yoon 2005), such as umbilical cord blood contains stem cells (Zhao et al. 2006), intestinal and hepatic stem cells (Yang et al. 2002; Lee et al. 2017). Despite the massive potential of stem cells in the treatment of patients with DM, a significant concern is the loss of novel beta cells immediately after portal vein transplantation that is in the range of 5-47% (van der Windt et al. 2007; Potter et al. 2014; Emamaullee and Shapiro 2007; Naziruddin et al. 2014). A current suggestion is co-transplantation of islets with different cell types, such as mesenchymal stem cells (MSC), bone marrow-derived MSC, endothelial colony-forming cells, and others (Kerby et al. 2013; de Souza et al. 2017; Borg et al. 2014; Corradi-Perini et al. 2017; Jung et al. 2014), to reduce losses of beta cells and increase their potential. This approach was shown to increase islets survival and function, and promote angiogenesis and better glycemic control due to the anti-apoptotic and pro-angiogenic effects of MSC (de Souza et al. 2017; Pathak et al. 2019). One clinical trial reported that co-transplantation of adipose tissue-derived insulin-secreting mesenchymal stem cells and cultured bone marrow to 11 DM patients achieved beneficial effects, such as decreased requirement for exogenous insulin and improved the health status of subjects (Vanikar et al. 2010).

3.2. Hyperbaric oxygen therapy in the treatment of DM

Hyperbaric oxygen (HBO) therapy (HBOT) is one of the methods used for the treating of numerous ischemic conditions accompanying DM such as cerebral ischemia, peripheral artery disease, gangrenous wounds (diabetic foot), ischemia and reperfusion injury,

central retinal artery occlusion, and other vascular complications (Visona et al. 1989; Karadurmus et al. 2010).

The main principle of the therapy is 100% O₂ inhalation under elevated atmospheric pressure from 1.6 to 2.8 ATA in special hermetically sealed hyperbaric chambers (Jain 2009). HBOT can be performed in individual hyperbaric chambers or multiple patient chambers (usually 2 to 14). In individual hyperbaric chambers compressed with pure O₂ patients are exposed freely in the supine position, whereas patients in multiple chambers inhale pure O₂ under hyperbaric conditions via a face mask or endotracheal tube. HBOT ranges from 5 to 40 days, and HBO treatments can last one to two hours, one to three times daily (Thom 1989). The initial effect of elevated gas pressure on the human body, at constant temperature, is an increase of hydrostatic pressure, which elevates the partial pressure of the gas and leads to a decrease in the volume of gas-filled spaces according to Boyle-Marriott's law. During HBO treatment, the solubility of O₂ in plasma is elevated more than 10 times (> 2000 mmHg), causing O₂ to diffuse rapidly to distant tissues (pO₂ in tissues is 200 - 400 mmHg) and thus contributes to tissue vitality altered due to the tissue ischemia (Thom 1989). HBOT is not recommended for people with lung disease (pneumothorax), respiratory, sinus and ear infections, fever, etc. Depending on the dose and length of HBOT, as well as the patient's condition, oxidative toxicity in the lung and nervous system, acidosis and hemolysis can occur (Saltzman 1965).

Numerous studies shown that HBO therapy also triggers a variety of molecular mechanisms in the body that lead to positive therapeutic effects in DM, such as: improvement of systemic hemodynamics and microcirculation (Zamboni et al. 1993; Mathieu 2006), angiogenesis acceleration (Marx et al. 1990), initiation of the antioxidant

defense (Ansari et al. 1986), increase in fibroblast proliferation and collagen synthesis (Yumun et al. 2016), inhibition of inflammation (Zhang et al. 2008; Benson et al. 2003) and reduction in the extent of atherosclerotic plaques (Karadurmus et al. 2010). Four to six hours after HBO treatment the partial pressure of O₂ remains elevated, and provides mitochondrial respiration and cell survival in a state of hypoxia (Thom 1989), inhibits pancreatic beta cell apoptosis (Zhang et al. 2008; Faleo et al. 2012), reduces leukocyte adhesion (Benson et al. 2003) and improves bactericidal activity of leukocytes (Hohn et al. 1976), contributing to the reduction of inflammation and vascular complications in patients with DM (Karadurmus et al. 2010). Furthermore, a recent study demonstrated the early beneficial effect of HBOT in the inflammation reduction by regulation of inducible nitric oxide (NO) synthase (iNOS) activity/expression in insulin-dependent DM patients (Resanovic et al. 2019a). Insulin dependent DM is linked with abnormal synthesis of NO which is associated with DM-related vascular complications (Rask-Madsen, King 2007; Fujimoto et al. 2005). HBO treatment causes down-regulation of iNOS expression via an Akt, ERK1/2, and NFκB mechanism, in insulin-dependent DM patients (Resanovic et al. 2019a). Also, HBO treatment exerts anti-inflammatory and anti-atherogenic effects in insulin-dependent DM patients, by improving the lipid profile and altering the composition of plasma fatty acid, as well as the expression of insulin-like growth factor binding protein 1 (IGFBP-1) (Resanovic et al. 2019b). The improvement in DM patients after HBOT significantly contributes to reduced vascular complications. Future studies related to the determination of both frequency and dose of HBOT with the maximum efficiency and minimum side effects in the treatment of patients with DM need to be conducted (Resanovic et al. 2019b).

3.3. Medicaments

After a long period of stagnation, diabetes pharmacotherapy exploded in the last decade. Defining new approaches in diabetes management, primarily non-insulin dependent ones or those who sensitize insulin action, enables the opening of new chapters in diabetes management (Grant and Kirkman 2015). Pandemics associated with diabetes complications and patient disabilities pressurize scientists from different areas to collaborate to establish more potent diabetes management (Rowley et al. 2017; Leon and Maddox 2015). Apart from innovations in the field of oral diabetes pharmacotherapy, some of the innovations concern insulin treatment. That is, innovations are also related to the formulation of insulin analogs with improved control of glycaemia and with lowered hypoglycaemia risk, as well as the development of non-parenteral route/s of insulin administration (Biester et al. 2017; Fink et al. 2018). Such innovations are placed into clinical practice through precisely defined recommendations signed by various endocrine and diabetes societies and associations, such as American Diabetes Association (ADA) (ADA 2018), American Association of Clinical Endocrinologists (AACE) (Garber et al. 2019), European Association for the Study of Diabetes (EASD) (Davies et al. 2018), the National Institute for Health and Care Excellence (NICE) (McGuire et al. 2016) and many others. Even though these recommendations have subtle differences, they are oriented towards a patient-centered approach and direct clinicians towards better and more uniform management of the patients (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016). Well-controlled diabetes apparently slow down the atherosclerotic process, which is the base of associated micro- and macrovascular

diabetes complications and major cardiovascular events, including ones with fatal outcomes (Diabetes Control and Complications Trial Research Group 1994; Zoungas et al. 2014).

We further summarize current recommendations for the management of DMT1 and DMT2 with a brief report on the effects and caveats for each pharmacotherapy group.

a) Pharmacotherapy of DMT1

Current recommendations are focused on individually tailored management of DMT1, consisting of dietary habits and physical activities changing, and administration of insulin. It is strongly advised to adapt insulin treatment to carbohydrate intake, pre-prandial glycaemia, and anticipated physical activity (ADA 2018; Handelsman et al. 2015; National Clinical Guideline Centre 2015).

The mainstay of DMT1 management is insulin, administered by pen device or continuous subcutaneous insulin infusion (CSII). The amount and number of divided insulin doses in children or adults immediately after DMT1 diagnosis is often lesser (1-2 divided doses), but often increase in time (Biester et al. 2017; Fink et al. 2018; Pickup 2019). In the last decades, there was a tendency to opt for insulin analogs with improved pharmacokinetics, pharmacodynamics, and safety compared to human insulin (Biester et al. 2017; Fink et al. 2018; Heinemann et al. 2017).

Rapid insulin analogs are active immediately after administration and with short-lived effects. Basal analogs have more prolonged effects than neutral protamine Hagedorn (NPH) human insulin regarding glycaemia control with lower hypoglycaemia risk. The usual overall daily dose of insulin is 0.5 IU/kg of body weight. During puberty and in exceptional circumstances, insulin requirements are higher. Overall, CSII is widely

recommended and favored when treating patients with DMT1. According to current recommendations, it can be used in patients older than 65 years (ADA 2018; Handelsman et al. 2015; National Clinical Guideline Centre 2015; REPOSE Study Group 2017; Beck et al. 2017).

In addition, pre-prandial inhaled insulin has been shown to be efficient as rapid insulin analogs (aspart) in regard to glycemic regulation and the risk of hypoglycaemia, but, its use in DMT1 patients is not widespread as it was expected (ADA 2018; Heinemann and Parkin 2018). Furthermore, the use of metformin, dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP-1 RA), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) is not Food and Drug Agency (FDA) approved, despite the treatments showing beneficial effects in obese DMT1 patients (ADA 2018; Handelsman et al. 2015; Livingstone et al. 2017).

Pramlintide, an amylin analog, is approved for the use of DMT1 adults, but exhibit higher risk for hypoglycaemia and obliged reduction of prandial insulin (Hieronymus and Griffin 2015). For patients with ineffective glycemic regulation or diabetics referred to renal transplantation, pancreas and islet transplantation could be the better treatment option (Gruessner 2011; Nakamura et al. 2019).

b) Pharmacotherapy of DMT2

An individualized approach to the management of DMT2 includes non-pharmacological and pharmacological activities. Non-pharmacological measures are usually the preferred treatment for DMT2 patients, but in the case where these measures fail to control DMT2, the patients' treatment regime would include pharmacological measures. Apart from the lifestyle change (nutrition and physical activity) and pharmacotherapy, an integral part of

DMT2 management is the screening for cardiovascular disease (CVD) risk factors as well as the detection of chronic micro- and macro-vascular complications (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

DMT2 management aims to achieve clinical and biochemical goals (actual profile and retrograde glycaemic regulation) to avoid hypoglycemic episodes and gain in body weight in obese patients and to control the risk of atherosclerotic CVD (ASCVD) (ADA 2018).

The management goals include adjusting HbA1C, morning glycaemia, and 5-point daily glycaemic profile to the patients' age, duration of DM, risk of hypoglycaemia, and the presence of comorbidities and chronic vascular complications associated with DM. The level of HbA1C is an essential marker for the assessment of retrograde glycaemic control in patients with DM. In DM patients with no comorbidities and low hypoglycaemia risk, HbA1C level $\leq 7\%$ (ADA 2018) indicates reasonable retrograde DM control for the period of the previous 90-120 days. On the other hand, in DM patients with severe comorbidities and considerable risk of hypoglycaemia, the acceptable level of HbA1C is $< 8\%$ (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016). A more stringent HbA1C goal of $< 6.5\%$ is set in some special populations of individuals suffered from DM (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

Pharmacotherapy of DMT2 is conducted as mono- or combination therapy. The therapy chosen depends on biochemical and clinical factors, existing comorbidities, as well as some potential side effects of administered drugs, which confirms the patient-centered approach as the cornerstone for DMT2 management.

c) Monotherapy of DMT2

For patients with newly diagnosed DMT2 having HbA1C <9% (6) or >6.5% (9), metformin is the initial therapy administered. Metformin daily dose of 1.5-2.0g is usually enough to keep glycaemia in the reference values. Metformin contributes to the decrease in body weight, and reduces risk of hypoglycaemia. Metformin use is associated with gastrointestinal side effects that are often transitional and dose-dependent. It is contraindicated in the case when the estimated glomerular filtration rate (eGFR) is <30ml/min. (Livingstone et al. 2017; Sanchez-Rangel and Inzucchi 2017).

In metformin-intolerant patients, acceptable alternatives are GLP1-RA, DPP-4i, alpha glucosidase inhibitors (AGi), and SGLT-2i. With the administration of agents, the risk of hypoglycaemia is lower, and there is no weight gain. Other alternatives are thiazolidinediones (TZD) and sulphonylureas (SFU) or glinides, but with considerable risk of hypoglycaemia and weight gain (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

d) Combination therapy for DMT2

In DMT2 patients with HbA1C >9% (ADA 2018) or $\geq 7.5\%$ (Garber et al. 2019; McGuire et al. 2016), as well as in those for whom metformin is not enough to achieve adequate glycemic regulation, another agent is added to the treatment regime. Metformin-intolerant patients are administered two or more agents with a complementary mechanism of action. There are fixed combinations that include metformin + DPP-4i/TZD/SFU on the market already. Additionally, metformin with modified-release could be a suitable alternative for patients' who are simple metformin-intolerant. According to the NICE guidelines (McGuire et al. 2016), the addition of agent/s to metformin or alternative agent in the case of metformin-intolerance in patients with HbA1C $\geq 7.5\%$ is called intensification of

DMT2 management. The acceptable level of HbA1C after management intensification should be <7%.

If despite the use of non-pharmacological measures and dual pharmacotherapy, HbA1C is $\geq 7.5\%$, basal insulinization should be the solution. Insulin treatment starts with a plan of its administration, and continued use of metformin is recommended in suitable and tolerant patients (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

It is further necessary to review the need for dose tapering or even the need for administration of other non-insulin glucose-lowering agents (McGuire et al. 2016). If the HbA1C $>9\%$, the patient should be instantly on dual oral treatment. Furthermore, if the patient initially presented with HbA1C $\geq 10\%$ or with glycaemia $>16.7\text{mmol/L}$ or is clinically symptomatic, combined treatment of insulin and oral antihyperglycemic therapy or even multiple insulin injections should be considered (ADA 2018). If an insulinization process of basal insulin introduction along with metformin and/or other non-insulin glucose-lowering agents fails to control DMT2, the addition of one or more doses of rapid-acting insulin or GLP-1RA should be considered (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016). Also, if a DMT2 patient is suffering from ASCVD, the addition of a CVD treatment agent such as empagliflozin, canagliflozin, dapagliflozin, or liraglutide should be considered (Arnett et al. 2019; Zelniker et al. 2019; Wiviott et al. 2019; Furtado et al. 2019; Marso et al. 2016).

1. Exenatide, liraglutide, and lixisenatide are GLP-1RA, peptides structurally homologous to the natural incretin glucagon-like peptide-1 (GLP-1), are currently available for the subcutaneous administration, but the great efforts are made to produce

oral daily and weekly GLP-1RA, **semaglutide**. The GLP-1RA stimulate glucose-dependent pancreatic insulin secretion as well as reduce glucagon secretion, and slow down gastric emptying. They also significantly reduce body weight and lower HbA1C levels. Some gastrointestinal side-effects could be encountered (nausea, vomiting, bloating, gastroesophageal reflux disease, and gastroparesis), but they are often transitional. The risk of hypoglycaemia is low. Also, in experimental studies on rodents, exenatide intake lead to hyperplasia of C cells and medullary thyroid cancer, while all the GLP-1RA caused pancreatitis. To summarize, GLP-1 RAs reduce body weight, rarely induce gastrointestinal side-effects, have low hypoglycaemia risk, and do not have negative effects on the bones, the appearance of diabetic ketoacidosis (DKA), and congestive heart failure (CHF) deterioration. Exenatide is not indicated in patients with eGFR<30ml/min. (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Deacon 2019).

2. Sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin are DPP-4i. That is, these treatments block the DPP4 enzyme involved in the degradation of incretins such as GLP-1 and gastric inhibitory peptide (GIP). Elevated incretin levels act on a simultaneous increase in glucose-dependent insulin secretion and decrease glucagon secretion. There is no convincing evidence regarding the higher risk of pancreatitis or pancreatic cancer with the use of DPP-4i. To summarize, DPP-4i exhibits neutral effects regarding hypoglycaemia risk and body weight change, and gastrointestinal side-effects are not frequent. DPP-4i effectively reduces albuminuria and do not have negative effects on the bones and the appearance of DKA. Saxagliptin use is not recommended for CHF patients. Also, renal dose adjustment is required when using all the DPP-4i except

linagliptin (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Deacon 2019; McGuire et al. 2019; Scirica et al. 2013).

3. Acarbose, miglitol, and voglibose are AGi. These treatments block the alpha-glucosidase enzyme involved in carbohydrate reabsorption in the gastrointestinal system. Side-effects associated with AGi use include bloating, diarrhea, abdominal cramps, and mild elevation of liver enzymes. To summarize, AGi exhibits neutral effects regarding hypoglycaemia risk and body weight change. Mild gastrointestinal side-effects are frequent. They do not have negative effects on the bones, CHF deterioration, and the appearance of DKA. Renal dose adjustment is not required (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Liu, Ma 2017).

4. Pioglitazone is a TZD that activates the PPAR γ receptors and through determined signal pathways, decreases insulin resistance in various tissues, predominantly in skeletal muscles (Yki-Jarvinen 2004). The clinicians are under pressure to precisely select the patients for their use because of some associated side-effects, such as body weight gain, fluid retention, higher risk of bone fractures, and bladder cancer (pioglitazone) (Phillips and Dunning 2003; Wang et al. 2017; Mehtala et al. 2019). To summarize, TZDs exhibit neutral effects regarding hypoglycaemia risk and body weight change when administered in moderate doses, and there are no associated gastrointestinal side-effects. They occasionally exhibit mild negative effects on the bones, CHF deterioration, and the appearance of DKA. Renal dose adjustment is not required, but TZDs are generally not recommended in any stage of renal failure due to fluid retention (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Yki-Jarvinen 2004; Phillips and Dunning 2003; Wang et al. 2017; Mehtala et al. 2019).

5. Sulphonylureas and glinides (gliclazide, glipizide, glimepiride, repaglinide)

mediate insulin secretion after binding to SUR Ki6.2 receptor, the sodium channel (Kalra, Gupta 2015). To summarize, SFUs and glinides exhibit significant effects regarding hypoglycaemia risk and body weight gain. There are no associated gastrointestinal side-effects. They, too, occasionally exhibit mild negative effects on CHF deterioration, but act on the bones and DKA appearance neutrally. Renal dose adjustment is required (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Wang et al. 2018; Harsch et al. 2018).

6. Dapagliflozin, canagliflozin, and empagliflozin are SGLT-2i that reduce proximal tubule glucose reabsorption by binding to the SGLT-2 receptors. The clinicians must be attentive towards some potential side-effects, such as ascending urinary infections, chronic and treatment-resistant urinary and vaginal candidiasis, the elevation of LDL-cholesterol, dehydration and hypotension, and mitigate presentation of DKA (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Wanner, Marx 2018; Lupsa and Inzucchi 2018). To summarize, SGLT-2i exhibit neutral effects regarding hypoglycaemia risk and contribute to bodyweight reduction. There are no associated gastrointestinal side-effects. SGLT-2i use is not indicated in patients with eGFR<45 (60 ml/min. Empagliflozin use requires special attention regarding its potential negative effects on the bones, as well as the use of all SGLT-2i regarding DKA appearance (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Singh and Kumar 2018). Some studies point out to positive effects of empagliflozin and dapagliflozin in cases with the occurrence of major CVD, ASCVD, and CHF deterioration (Arnett et al. 2019; Zelniker et al. 2019; Wiviott et al. 2019; Furtado et al. 2019).

In exceptional circumstances, when it is impossible to control DMT2 with the usual mono/dual/combined therapy, **colesevelam** (Ooi and Loke 2014) and **bromocriptine** (Lopez Vicchi et al. 2016) could be used. Their mechanism in blood sugar lowering is not known, but the risk of hypoglycaemia is low.

Conclusions

The future perspectives in diabetes management should be traced into two simultaneous paths. The first one is to improve the pharmacokinetics and pharmacodynamics of already available drugs aiming to normalize blood sugar levels and to reduce some already noticed side effects. The second one is to enhance the present and to innovate new technologies based on unraveled conundrums in natural diabetes history. The resultant of the paths mentioned above is diabetes management adjusted to each individual. Thus, medical societies must reorganize and therefore provide prevention and more accurate control of diabetes and associated comorbidities. The main objectives of upcoming studies are to progress the existing therapies and develop new approaches to achieve normoglycaemia, simultaneously with the reduction of side effects of present treatment modalities. The focus on diabetes management should be an individual approach to each patient.

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