Journal of Mind and Medical Sciences

Volume 10 | Issue 2 Article 6

2023

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Recommended Citation

Socea, Bogdan; Silaghi, Adrian; Rebegea, Laura Florentina; Balan, Daniela Gabriela; Balalau, Cristian; Tenea-Cojan, Tiberiu Ștefăniță; Mihai, Doina Andrada; and Paunica, Ioana (2023) "Diabetes mellitus: interdisciplinary medical, surgical and psychological therapeutic approach," *Journal of Mind and Medical Sciences*: Vol. 10: Iss. 2, Article 6.
DOI: https://doi.org/10.22543/2392-7674.1445
Available at: https://scholar.valpo.edu/jmms/vol10/iss2/6

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Journal of Mind and Medical Sciences

https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/

ISSN: 2392-7674

Diabetes mellitus: interdisciplinary medical, surgical and psychological therapeutic approach

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ABSTRACT

Diabetes mellitus is a complex and widespread metabolic disease, having extremely complex implications (biological, psychological, social) for patients. Understanding the pathophysiology of diabetes (majorly influenced by various factors such as genetic predisposition, age, lifestyle choices, etc.) is essential for the prevention of this condition and the establishment of effective treatment strategies. The latest and relevant literature data related to the epidemiology, pathophysiology, and treatment of diabetes are presented, after an exhaustive review of the articles published on this topic and indexed in the WOS, PubMed, Scopus and Google Scholar databases. Preventing or delaying the onset of diabetes can be achieved in some patients with type 2 diabetes. After onset, treatment of diabetes is complex, involving a comprehensive approach (pharmacological interventions, lifestyle changes, surgical interventions in selected cases, as well as psychological support), depending on the stage of the disease and possible associated complications. Finally, diabetes is often asymptomatic in the initial stages, so an early diagnosis remains the essential element for the best subsequent therapeutic control.

Category: Review

Received: June 18, 2023
Accepted: July 24, 2023
Published: October 25, 2023

Keywords:

diabetes mellitus, interdisciplinary, medical, surgical, psychological, therapeutic, approach

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Introduction

Diabetes mellitus (DM) is a metabolic disease with a high incidence among the population, being characterized by the presence of high levels of glucose in the blood. Hyperglycemia has both direct consequences on the cells of the body, as well as through the alternative pathways of glucose metabolism [1]. Historically, diabetes has been divided by age of onset into juvenile diabetes (type 1 diabetes) and adult-onset diabetes (type 2 diabetes), the latter being secondary to increased calorie intake from various sources (sugars or lipids). Until the discovery of insulin, diabetes mellitus type 1 was a fatal disease, secondary to the chronic catabolic state and the frequent occurrence of severe episodes of ketoacidosis (newborns in rare cases exceeded 2 years) [2,3].

Most cells in the body suffer when exposed to high blood sugar levels. The complications associated with this disease are multiple, with or without clinical expression, they can appear earlier or later and in different degrees of severity. Microvascular lesions in the persistent hyperglycemic syndrome lead to different forms of manifestation such as retinopathy, nephropathy or diabetic neuropathy [4]. Regarding the large vessels (placed at cerebral, cardiac or peripheral level), the complications of diabetes can lead to myocardial infarction, strokes, and minor or major amputations secondary to the occlusion of peripheral arteries [5].

To cite this article: Socea B, Silaghi A, Rebegea LF, Balan DG, Balalau C, Tenea-Cojan TS, Mihai DA, Paunica I. Diabetes mellitus: interdisciplinary medical, surgical and psychological therapeutic approach. *J Mind Med Sci*. 2023;10(2):217-236. doi:10.22543/2392-7674.1445

In addition to all these direct effects of increased blood sugar, there are also a number of psychological changes that occur in these patients. These can be secondary both to the increase in blood sugar and to the treatment of this disease burdened most of the time by high costs, painful and repeated interventions, or various complications that may occur (which often led to the inability to move or take care of own body) [6].

The management of diabetes is complex, reducing the glycemic level being the main goal in controlling the disease. There are also therapies aimed at reducing the preventable mortality rate, as well as increasing the patient's quality of life that can lead to a life as close to normal as possible. Thus, multiple medical, surgical and psychological methods have been developed, sometimes it is necessary to combine them to obtain favorable results [7].

The present study is a review with the objective of identifying the most recent data from the literature regarding epidemiology, etiology, physiopathology and the new treatment methods (medical, surgical and psychological) that have appeared recently.

Discussions

Epidemiology

With the increase in life expectancy, the economic development of countries and the adoption of a different type of diet, there has been an increase in the incidence of diabetes. From a pathophysiological point of view, a consensus has been reached that divide high glycemic level according to age, the main cause and risk factors in diabetes type I, type II, hyperglycemia associated with pregnancy, pancreatic disorders or other endocrinopathies [8]. Thus, in 2014, 422 million patients were registered globally with diabetes, with an increase in prevalence especially in underdeveloped and developing countries (for example, an increase in Africa from 3.1% in 1980 to 7, 1% in 2014) [9].

The diagnosis of diabetes is usually made late, because the appearance of high blood sugar is poorly expressed clinically or even asymptomatic. Thus, 45.8% of all cases of diabetes that occur in adults are undiagnosed from the onset, so they are much more exposed to the development of complications than those who receive treatment. Costs associated with late-diagnosed forms are 3 times higher than in the general population, reaching $673 billion for the underlying disease and associated complications [10,11].

Most patients with diabetes are found in Asia, China together with India (totaling over 180 million), followed by the USA (where 30.2 million people have high blood sugar levels), Brazil (with 12.4 million) followed by Indonesia and Mexico (having 12 and 10.3 million patients respectively). 95% of these cases are considered to be type II diabetes, the remaining 5% are attributed to type I diabetes [9]. In terms of distribution within different populations, both genetic characteristics and living environment have a major contribution. In the US, there is an increase of approximately 1.5 million patients with diabetes per year, with the prevalence of diabetes in non-Hispanic blacks at 17.7%, especially in the male population, followed by Hispanics, Asians, and whites [12].

Type I diabetes appears predominantly around the age of 15, with a high incidence in developed countries such as the USA, Great Britain, China, Brazil or Nigeria, and with global variations between 0.13 and 1.61 respectively per 100,000 inhabitants [13]. The male population is usually the majority, exceeding the percentage of 50% in countries with a Human Development Index of over 0.700, equal values being observed in less economically developed countries. Lower values appear in the non-European population compared to the European one [11].

Diabetes mellitus was the direct cause of death in 6.8% of cases, with approximately 5 million deaths/year associated with acute complications of hyperglycemia, with an increasing number being recorded today. Along with the premature death of the population, diabetes mellitus is associated with an increased risk of disability, ending up being in the first 5 entities that cause its appearance in the population aged between 20 and 70 years (it is responsible for approximately 143 million patients with impairment of activity and quality of life [14].

Gestational diabetes is defined as the presence of glucose intolerance associated with hyperglycemia detected in any trimester of pregnancy, without these features being present before pregnancy [15]. Women and babies who develop during this period are subject to immediate and long-term complications, with the risk of developing type II diabetes after pregnancy being over 60% in the first 16 years after the event [16]. In Europe, the prevalence of diabetes in the pregnant population reaches values of 20% [17,18]. Recent data show a 39% rate of gestational diabetes in obese or overweight women in Western Europe, with prevalence rates ranging from 24% in the UK to 52% in Denmark. Much lower rates, between 2-6% are observed in the northern area of Europe or in the Mediterranean Sea basin [18].

The main complications that can occur in gestational diabetes are: the occurrence of preeclampsia or eclampsia, the presence of a macrosomic fetus, increased rates of caesarean section or low birth weight with the admission of the newborn to the neonatal intensive care unit. All these parameters were influenced by the presence of elevated glycemic levels, thus the rate of hypertension associated with pregnancy reached 17%, along with high birth weight that occurred in 18.5% of cases and premature birth resulted in a rate of caesarean section in this population of 40.2% of cases. Females born to these mothers with high glycemic levels required admission to the intensive care unit in 6.65% of cases [19].

Type II diabetes is secondary to specific causes and can occur in a series of endocrinopathies such as excess hyperglycemic hormones (growth hormone, cortisol, catecholamines), in the context of treatments with protease inhibitors for HIV, antipsychotics administered in psychotic/schizoaffective disorders or from an immune cause (immune checkpoint inhibitors for some forms of cancer). Treatment of the underlying disease may result in resolution of elevated glycemic levels, and when this is determined by treatment, a risk versus benefit assessment must be considered [19].

Pathophysiology

Type I diabetes is characterized by low insulin secretion secondary to accelerated destruction of pancreatic β-cells by autoantibodies, which will eventually lead to hyperglycemia and acidosis as a result of low blood insulin levels. The destruction of pancreatic β-cells begins with the loss of tolerance of the immune system, being considered foreign and attacked by immune cells, a process controlled by T cells. Thus, the identification of the steps leading to the attack of β-cells by specific antibodies and immune cells may be sooner or later identified and modified in the sense of stopping aggression and thus preventing the onset of diabetes [20].

The link between immune cells and type I diabetes was highlighted in some patients who had certain types of antigens of the Human Leukocyte Antigen (HLA) system and elevated blood sugar levels. Later through research on the human genome, HLA class II was identified as a genetic risk factor, being responsible for 50% of the cases of type I diabetes, which suggests that the presentation of a certain peptide to the immune system is involved in the pathogenesis of this diseases [21]. Genetic factors that predispose to type I diabetes include genes that control immunity, tyrosine phosphatase, non-receptor type CTLA4, and lns [22]. Thus, in most cases type I diabetes can be a polygenic syndrome, but they are also found in isolated cases where only a single gene can be involved, such as the Autoimmune Regulator gene associated with autoimmune polyglandular syndrome type 1 [23].

During the course of the disease, a series of antibodies against insulin, glutamate decarboxylase, insulinoma antigen 2 or zinc transporter 8 may appear, which may represent the sign of autoimmunity, their level can be determined in the patient's plasma and correlated with the severity of the disease [24]. The synthesis of these autoantibodies could be influenced by CD4+ and CD8+ T cells, which are found in the peripheral blood, in the pancreatic tissue and even in the peripancreatic lymph nodes, with the difference that in the case of patients with type I diabetes the cells have activity against β cells [25.26]. The presence of these autoreactive species in the peripheral blood is quite small and is similar to the concentration found in a healthy individual, the only difference being an abnormal activity in the periphery of CD 8+ cells, secondary to a series of changes that occur during their activation [27]. These CD8+ cells have functional characteristics different from normal ones, that is they show a low epitope affinity for HLA complexes and low interaction with antigen-presenting cells. Some localized changes in T receptors do not elicit an extensive immune response when interaction with the HLA-epitope complex is present. All this is the consequence of their incomplete maturation during development at the thymic level [28-30].

Various extrinsic factors have been proposed for autoactivation of the immune system and pancreatic β-cell destruction. Metabolic stress, viral infections or the presence of pro-inflammatory agents that reach the pancreatic tissue from the digestive tract through different pathways are usually involved in the autoimmune response [31]. Thus, during a viral infection, pancreatic β cells express adhesion factors and receptors, including coxsackievirus and adenovirus receptor (CAR). They have been identified in insulin-containing granules, leading to a vulnerability of pancreatic tissue to infection with coxsackievirus B4 [32] and could trigger type I diabetes in patients who had enterovirosis with such a virus. For other viral particles, such as rotavirus and cytomegalovirus, the pancreatic cell response may be similar to coxsackievirus B4 infection [33,34].

Other factors involved in the onset and worsening of type I diabetes are diet and gut microbiota. One of the roles of the bacterial population of the digestive tract is represented by the modulation and differentiation of local immune cells, in order to maintain homeostasis which is achieved through cellular immunity but also through the short-chain fatty acids synthesized by it [35]. The roles of fatty acids are varied, from direct inhibition of neutrophils and dendritic cells (through the synthesis of antimicrobial peptides by lymphoid cells or pancreatic B cells), to the role of moderating the immune response generated by T cells (through inhibition of histone deacetylase), as well as activation of pathways mammalian target of rapamycin (mTOR) [36]. Experimental studies on mouse populations demonstrated the protective role of these antibacterial cytokines against the onset of type I diabetes and the ability of short-chain fatty acids to decrease the synthesis of cellular messengers that could cause pancreatic β-cell destruction [37].

The patient's diet can influence the onset of type I diabetes both directly and through the microbiota. Thus, a low-gluten diet during pregnancy may lead to low rates of autoimmune diabetes in newborns [38]. Administration of vitamin D, omega-3 fatty acids did not have clear results in terms of decreasing the risk of developing type I diabetes [39].

In type II diabetes there is a dysregulation of the control mechanisms between the glycemic level and

insulin secretion, thus leading to hyperglycemia [40]. One of the main causes of this phenomenon is β-cell dysfunction, which leads to inadequate secretion compared to the need to maintain an adequate glycemic level. At the same time, there is an increase in glucose synthesis in the liver and a decrease in its use in muscle and adipose tissue, secondary to the inability of specific receptors to respond to these stimuli, a phenomenon called insulin resistance [41].

The synthesis of insulin at the level of pancreatic β cells is done in stages by conformational changes of proinsulin and keeping the active form in vesicles that are secreted when needed. The main stimulus for its release from blood cells is glucose via the glucose transporter, a cation transport protein that causes the change in the ATP/ADP ratio that closes ATP-dependent potassium channels. This subsequently leads to an increase in the concentration of ATP, but also the accumulation of intracellular calcium that will mobilize the granules in which insulin is stored and thus they will migrate to the cell membrane where they will be eliminated by exocytosis [42]. Other stimuli that cause the release of insulin from cells are represented by large amounts of amino acids, fatty acids, hormones [43] and also extracellular cAMP or ATP by influencing intracellular calcium levels [44,45].

If there are elevated levels of blood glucose or serum lipids secondary to persistent food excess, a state of chronic inflammation is observed and with it a series of consequences such as: oxidative, amyloid and metabolic stress, which will lead to the loss of the integrity of the pancreatic islet tissue [46]. Lipotoxicity, glucotoxicity, and glycoprotein toxicity occur in the context of obesity and metabolic stress secondary to activation of the cellular apoptotic unfolded protein response (UPR) at the β-cell level [47]. The increased level of fatty acids can cause inhibition of the sarcoplasmic reticulum with decreased intracellular calcium mobilization. Persistent glycemic status may increase β-cell synthesis of proinsulin and islet amyloid polypeptides (IAAPs), which will lead to a three-dimensional misfolding of proinsulin, with its accumulation in the cytoplasm increasing oxidative stress that will ultimately lead to a cascade of proapoptotic elements with tissue destruction and chronic inflammation [48].

Another consequence of hyperglycemia and glucotoxicity is the increased synthesis of reactive oxygen species (ROS) that will generate an inflammatory syndrome and increased oxidative stress. Excess ROS led to an inactivation of mitochondria that will not be able to metabolize superoxide ions. They are directly involved in the pathogenesis of diabetes, so they are responsible for the formation of advanced glycation end products (AGEs) by stimulating the polyol pathway. Thus, a series of changes in normal cell physiology occur, including for example increased expression of AGE receptors and activation of protein kinase C and its isoforms [49,50]. Secondary to these metabolic products, a state of hypoxia and ischemia occurs, which will lead to the release of inflammatory markers, and their activity can lead to neo-formation of vessels and irreversible changes in the normal structure of tissues, even if the glycemic level will normalize [51].

Reduced physical activity predisposes to obesity and type II diabetes. A variable degree of systemic inflammation can occur which will lead to the release of cytokines such as IL-6, TNFα and IL-1 into the bloodstream, known as metabolic inflammation [52]. Elevated levels of IL-1 directly affect pancreatic β-cells by releasing a large amount of nuclear factor kappa-enhancer of activated B-cell light chain (NF-κB), which will lead to a decrease in their ability to release insulin in blood flow and further induce apoptosis. If the patient decides to lose weight, there is a sensitization of the tissues to insulin, thus improving the glycemic level and reducing the overall cardiovascular risk. The underlying mechanism for this is the release of anti-inflammatory cytokines such as IL-1 and TNF-α antagonists and the release of antioxidant factors such as glutathione, which will neutralize free radicals released as a result of aberrant metabolic pathways [53-55].

Similar to type I diabetes, the microbiota has a determining role in the occurrence of type II diabetes [56]. A diet rich in fatty acids causes an increase in the level of lipopolysaccharide synthesized by intestinal bacteria, which will lead to local inflammation and insulin resistance along with a change in the ratio of bacteria present at this level [57]. The resulting dysbiosis can cause a decrease in the production of amino acids and trimethylamine that will cause the alteration of blood sugar regulation mechanisms, thus favoring the onset of type II diabetes [58,59].

During pregnancy, a series of changes occur that favor the development of the fetus. In the first period of pregnancy, there is a general sensitization of the tissues to insulin, which will determine the capture of glucose in the tissues secondary to the increased need [60]. Following the increased levels of estrogens, cortisol, leptin, progesterone and placental growth hormones, insulin resistance will appear [61], which will determine a higher glycemic level necessary for fetal growth. For a good glycemic control, it is necessary to compensate the function of the pancreatic β-cells. In normal pregnancy, pancreatic islet hypertrophy and hyperplasia may occur along with increased insulin secretion [62].

In the case of gestational diabetes, the damage can be multifactorial, affecting all phases of insulin synthesis and release. Most often, there are genetic lesions of the

potassium channel KQR-like 1 and glucokinase. In the case of minor deficits, any stressful factor can cause diabetes, especially pregnancy. In addition to the genetic damage of these patients, the above-normal glycemic levels cause the appearance of glucotoxicity, which negatively influences β-cell function with decreased insulin secretion and stimulation of apoptosis, thus forming a vicious circle in which gestational diabetes occurs [63].

The placenta, through the synthesis of the hormones and cytokines it secretes, causes hyperglycemia and later, in selected cases, gestational diabetes. Transplacental glucose transfer occurs via GLUT1 without the need for insulin [64]. The changes observed in the placenta of babies born to mothers who had gestational diabetes were mainly in the area of lipid metabolism compared to that of glucose (67% vs 9%) [65], a fact confirmed by the relationship between maternal obesity, glucose and excess growth of fat sizes [66].

A number of products such as Bisphenol A have been associated with the presence of elevated glucose levels in pregnancy by altering methylation at the cellular level, thus altering the signals received by the placenta [67].

Elevated glycemic levels in patients' plasma cause a series of changes in the structure and physiology of cells through the aberrant activation of various metabolic pathways. Aberrant activation of protein kinases C has been observed in association with increased formation of polyols, hexosamines, glucose autoxidation, and elevated levels of advanced glycation end products, all of these metabolic adaptations serving to reduce elevated glycemic levels [68].

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Protein kinases are a family of proteins involved in the growth, differentiation and modulation of vascular permeability being an important factor for the neoformation of blood vessels [69]. In the event of an increase in the glycemic level, there is an increase in the activity of these molecules in various tissues such as the myocardial, retinal, or renal, etc., which will lead to complications that influence the formation of polyols, thus amplifying the changes in the cell structure [70,71]. The cellular mechanisms by which these changes occur are the activation of different growth factors such as transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). All these factors will lead to the exacerbation of the extracellular matrix, which may play an important role in the progression of chronic diseases such as diabetic nephropathy [68].

Polyols are products that result in an alternative way of glucose metabolism mediated by 2 enzymes: aldose reductase and sorbitol dehydrogenase using Nicotinamide adenine dinucleotide phosphate (NADPH) as catalysts [72]. Physiologically, these 2 enzymes are involved in the formation of fructose used in different organs such as: kidneys, intestinal cells and spermatocytes [73]. Sorbitol, one of the polyols, can cause changes in ATP function and thus (due to the strong electronegative charge) changes in cellular osmotic pressure [74]. Being a polar molecule, sorbitol cannot easily cross the cell membrane accumulating at this level, mainly in the retina, kidneys and Schwann cells, which causes the increase of osmotic pressure and subsequently the attraction of water increasing their volume and destroying the cells [75]. Thus, cataracts appear in diabetic patients, with much higher rates and in a shorter time than the healthy population, enzymes and renal tubular cell dysfunction, but also poor myelination of axons due to the poor differentiation of Schwann cells through the low expression of Insulin-like growth factor 1 (IGF-1) receptors [76]. Through the excess use of NADPH and the inability to regenerate it, there is a surplus of NADH that causes changes in lipid metabolism, the formation of growth factors and the activation of protein kinase C, causing increased oxidative stress.

Advanced glycation end products (AGEs) represent non-enzymatic reaction products between free amino groups of various compounds and glucose or aldehydes [77]. These products are responsible for some of the micro- and macrovascular complications of diabetes. A specific phenomenon is observed in structural proteins such as collagen, where the reversible reaction between amino groups and sugars forms a covalent bond that cannot be easily broken, thus causing changes in the spatial structure of these structures. The clinical symptom that occurs is atheroma plaque formation along with basement membrane thickening, reduced elasticity and subsequent tissue dysfunction [78]. At the cellular level, a number of cellular signaling mechanisms are affected. Nitric oxide-induced vasodilatation through its secondary inactivation to the pro-oxidant environment, activation of nuclear factor kB, cellular expression of adhesion molecules and activation of transmembrane transport proteins such as Rac type can cause systemic inflammation, endothelial dysfunction, atherosclerosis and thrombosis [79].

In large quantities, glucose can undergo autoxidation phenomena that will lead to the formation of reactive oxygen species such as H_2O_2, malondialdehyde or

methylglyoxal, glyoxal [80]. The effects of these highly reactive products are the intensification of oxidative stress, and the resulting substances can change the spatial structure of proteins, because the reactive carbonyl species contained in it can bind to arginine and lysine, which will cause the same result as the large amount of AGEs [81].

Treatment

Secondary to the high level of blood sugar, micro and macrovascular complications appear, thus increasing the general cardiovascular risk, premature aging of the tissues secondary to oxidative stress and the decrease in the quality of life due to the presence of various conditions that can cause a marked decrease in visual and locomotor activities. Acute complications such as hypoglycemic or hyperglycemic coma can be life-threatening for patients, direct consequences of inadequate insulin synthesis and release. Thus, DM treatment requires a multidisciplinary approach in controlling metabolic and cellular abnormalities and their consequences [82].

The main goal of DM treatment is to normalize the glycemic level, so since the development of insulin, numerous antihyperglycemic substances have been introduced, which function both as insulin agonists and as secretion stimulators or as sensitizers of insulin receptors in various organs. Most of the time, combinations of these are used for adequate blood sugar control. Rapid-acting insulin and its analogs act during meal periods by reducing postprandial blood glucose, and prolonged-release insulin has a similar action to continuous insulin release to maintain an adequate blood glucose level [83]. In addition to these direct methods of insulin administration, a series of adjunctive measures must be taken, such as lifestyle modification, administration of compounds that reduce oxidative and general cardiovascular stress and thus reduce the need for medication and improve quality of life [84]. Thus, the administration of insulin solves only part of the problem, the disease will continue its evolution and large doses of drugs will be needed for the same result, therefore a series of adjuvant therapies have been developed that have the role of either sensitizing the tissues, to respond better to insulin stimulation or to increase the release of insulin from stores [85].

Medical treatment

Insulins

Basal insulin analogs have the ability to maintain a glycemic level as constant as possible, with fewer episodes of nocturnal hypoglycemia [86], with a level closer to the limit value in the case of glycosylated hemoglobin. Regarding the different preparations available, glargine is an insulin analogue that precipitates at the level of the subcutaneous tissue secondary to the constant pH of this level, causing the formation of dimers and monomers, which will lead to a constant release [87]. Compared to Neutral Protamine Hagedorn (NPH), insulin glargine has much lower peak release levels and minimal individual variability [88]. The rate of administration of the 2 substances is different, so a single dose of Glargine is similar to taking 2 doses of NPH insulin in terms of long-term blood sugar control. Hypoglycemia, which can occur with inadequate dosing of insulin preparations, showed fewer hypoglycemic events, particularly at night, for NPH-insulin. However, the satisfaction level of patients using Gla-100 is much better than for NPH-insulin [89].

Detemir is a product that contains a fatty acid chain that favors the formation of dihexamers that can attach more easily to albumin. Thus, there is a slower release of it from the injection site, with less individual variability in the pharmacodynamics of the prepared insulin and with a longer duration of action [86]. Compared to NPH insulin, Detemir has a better safety profile, with a lower risk of hypoglycemia, including at night, and with much smaller daily variations. These characteristics are similar to those of Gla-100, but with a requirement of 2 doses per day [90], with the effect diminishing after 12 hours [91]. In the long term, the glycemic level monitored by glycosylated hemoglobin was similar (8.8 Glargine vs 8.9 Detemir), which shows no major differences between the efficiency and effectiveness of Detemir vs Gla-100 [86].

Degludec is a newer generation insulin product in the form of a hexamer that dissociates locally into monomers and is subsequently absorbed and circulates in the plasma via albumin. Comparative results with GLA-100 are better in terms of nocturnal hypoglycemia and glycemic level [92], but with similar results in terms of maintaining basal glycemic level [93].

The method of basal insulin administration is important in disease control. Continuous subcutaneous administration mimics the continuous basal secretion of pancreatic cells, which reduces the risk of hypoglycemia compared with multiple-dose administration based on circadian cycle variations [94]. In addition, a better quality of life and a better degree of satisfaction were observed in the first case [95].

Fast insulin or during the meal is used most of the time in the case of a sudden increase in the glycemic level, such as in the case of a rich meal or in case of complications. It is often administered as a bolus in combinations of short-acting insulin and rapid analogues, depending on the amount of carbohydrates a patient consumes with a meal, the glycemic level before the meal and the possible physical activity he will perform [86].

The use of rapid-acting human insulin compared with rapid-acting insulin analogues such as lispro and aspart showed better glycemic control and fewer complications than insulin analogues [96], the main factor monitored being the risk of nocturnal hypoglycemia [86]. Concomitant administration of human insulin and

glargine provided long-term inadequate glycemic control compared to administration of the analog + glargine, with a significant decrease in glycosylated hemoglobin when administered 30-45 minutes before a meal. The risk of hypoglycemia for these 2 treatment strategies is similar. In addition to the classic method of bolus administration, the continuous infusion administration of prandial insulin showed similar glycosylated hemoglobin values for analogs, namely human insulin [97].

New formulas of insulin preparations - smart insulins

The concept of smart insulins is based on the ability of some systems to release insulin endogenously under conditions of hyperglycemia and to decrease the insulin release concentration if the blood glucose concentration decreases [98]. The system that controls the release of insulin relies on a sensor, a chemical that can change its chemical or physical structure that can trigger the release of insulin or other molecules [99]. Insulin delivery systems are largely based on polymers that form an impenetrable matrix under normoglycemic conditions, but once the glycemic level rises above a certain level, structural changes occur, such as swelling or shrinking, which alters the permeability to insulin, allowing it to release the nanostructure [100]. The factor that changes the spatial structure of the matrix is in many cases the pH for polymers such as poly(2-dimethylamino), poly(acrylic acid), hyaluronic acid, but also hypoxia or oxygenated water resulting from the oxidation of glucose with a better control in regarding the release of incorporated substances [101].

An advantage of incorporating insulin into polymer macrostructures is the ability to add multiple types of insulin, within multiple polymer types, which will result in on-demand release, thus providing better stability and response when a stimulus [102].

Insulin therapy devices

Since the discovery of insulin, the predominant method of administration has been through subcutaneous injections, and with the development of technology there have been a number of devices such as smart pens, pumps and needle-free devices, as well as alternative ways of administering insulin that are less invasive. Smart insulin pens are devices that can be connected via Bluetooth to an application on any smartphone device through which the dose of insulin can be better adjusted according to physical activity and carbohydrate intake [103]. Recorded data can be sent to a server where the attending physician and patient can better dose the amount of insulin based on the patient's history. One of the disadvantages of subcutaneous administration is the repeated puncturing of the integuments. Insulin jet injectors represent a new method of administration by which a high-pressure jet pierces the skin, and the insulin reaches the level of the subcutaneous tissue where it is absorbed. The advantages of this system are represented by a better control of postprandial blood glucose and a shorter duration until the action takes place with the risk of ecchymosis in the case of too high pressure [104].

Among the insulin pumps developed on the market, the insulin patch-pump system is the newest model, which presents several features that make it superior to other models, such as simplicity of use or the absence of skin penetration with a sharp object (delivering insulin through a packet) [105]. Another way of infusing insulin through the pump is the peritoneal one, recommended for patients with skin and subcutaneous tissue lesions and whose insulin administration may have variations, with very good results in terms of glycemic control but with the risk of infection at the level catheter [106].

The advantages of using insulin pumps are the low incidence of hypoglycemic episodes secondary to a better dose of insulin, a better quality of life secondary to the more flexible lifestyle it brings, and the small number of injections required to administer the treatment. The main disadvantage of these devices is the high maintenance and purchase price together with possible infections and irritation at the insertion site [107].

The artificial pancreas is a pump that administers insulin based on the blood glucose level at a given time. Thus, a sensor is used that measures blood sugar, the data being sent to a computer that analyzes the result received and, according to an algorithm, determines the release of the substance [102]. The efficiency and safety offered by these systems depend on the algorithm underlying insulin delivery, so the addition of a hypoglycemia control system leads to lower rates of nocturnal hypoglycemia compared to pumps that deliver insulin only according to the electrical signal received from the sensor (the algorithm can anticipate a possible decrease in the glycemic level) [108].

From this idea was developed the bionic pancreas, which is a dual infusion pump that releases both glucagon and insulin into the bloodstream, controlled by a smartphone app. By measuring blood glucose over a short period of time, along with other factors such as previous blood sugar levels, the amount of insulin administered, the level of activity and carbohydrate intake, the artificial intelligence determines the amount of insulin needed and subsequently releases glucagon if there is excess. By using these smart devices, patients' quality of life has increased significantly, with better glycemic control (fewer episodes of nocturnal hypoglycemia with constant glycosylated hemoglobin), but with increased acquisition and maintenance costs [109].

Other hypoglycemic treatments

In addition to the classic treatment with insulin, which has the role of completely replacing pancreatic function, a number of other substances have been developed with the aim of lowering blood sugar levels, reducing body weight

in obesity and general cardiovascular risk [110]. All of these have been classified as non-insulin treatment, acting either by stimulating the release of insulin from the pancreas, by improving the affinity of cells for the hypoglycemic hormone, by decreasing the formation of glucose in the liver, or by inhibiting glucose transport [111].

Biguanides and thiazolidinediones are substances that have the ability to reduce insulin resistance and at the same time positively influence other abnormal metabolic processes such as aberrant lipid metabolism and atherosclerosis [112]. Metformin, a biguanide, has the ability to decrease hepatic glucose synthesis by activating AMP-activated protein kinase (AMPK) at the mitochondrial level, with an increase in tissue sensitivity to insulin due to the influence of tyrosine kinase pathways and acceleration of insulin secretion at the β-cell level [113]. All these effects are associated with a better proliferation of type I collagen at the bone level with the ability to maintain normal bone density but also with a greater risk of developing metabolic acidosis or diarrhea [114,115].

Thiazolidinediones are proliferator-activated receptor-γ (PPAR-γ) agonists that have effects similar to biguanides, causing an increase in insulin secretion through stimulation of pancreatic β-cells and a sensitization of peripheral tissues, especially liver and adipose, to hypoglycemic hormone. The hypoglycemic effects are associated with a decrease in circulating fatty acid levels and an anti-inflammatory effect, which will lead to a decrease in overall cardiovascular risk, but with a higher risk of weight gain secondary to the stimulation of adipocyte formation from mesenchymal stem cells and fractures by primary differentiation of osteoblasts into osteoclasts, secondary to PPAR-γ receptor activation [83].

The category of insulin secretagogues includes sulfonylureas and meglitinides, which have the ability to stimulate pancreatic β-cells at various stages of insulin formation. Sulfonylureas cause an increase in insulin release by binding to the transmembrane receptor SUR-1 that controls the ATP-dependent K channel that closes and releases preformed insulin regardless of the glycemic level. Associated adverse reactions are mainly represented by marked hypoglycemia, especially in the elderly who have multiple drug combinations, impaired renal or hepatic function, marked weight gain, skin rashes or porphyria [83].

Meglitinides are synthetic antidiabetics that also bind to pancreatic β-cell K channels, but with a much weaker effect than sulphonylureas [116]. The main use of meglitinide is to control postprandial blood glucose by increasing insulin secretion [117], but with fewer side effects (such as hypoglycemia or cardiovascular events) due to its shorter half-life [118].

Glycosidase inhibitors are nitrogen-rich substances that have the ability to inhibit the breakdown of disaccharides and oligosaccharides in glucose, and thus its absorption at the intestinal level is lower with a decrease in postprandial blood glucose [119]. An improvement in pancreatic β-cell function was observed after initiation of treatment. The overall effect will lead to weight loss, improvement in hypertriglyceridemia and systemic blood pressure, reducing overall cardiovascular risk, but with digestive symptoms such as diarrhea, flatulence, and vomiting secondary to the processing of sugars by the microbial flora in the colon [120].

Incretin treatment was based on the ability of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to stimulate pancreatic β-cells by coupling to G protein-coupled receptors that will close or open the K-ATP channel, along with stimulation of β-cell proliferation, inhibition of apoptosis and glucagon secretion. The release of these molecules is controlled by nutrients in the form of glucose and carbohydrates, during fasting the level is low but after ingestion of food they can reach high values [121].

Thus, by administering GLP-1 receptor agonists, such as dulaglutide, albiglutide and semaglutide [122], there is a decrease in glucagon synthesis and secondary hepatic glucose production, with a significant improvement in pancreatic β and α cell function, along with weight loss through decreased appetite due to delayed gastric emptying [123]. Due to the effects of GLP-1 agonists, they are recommended as the first line of treatment for diabetic patients with cardiovascular risk factors, preventing heart attacks and strokes by maintaining good glycemic levels. After the introduction of such a product, the level of glycosylated hemoglobin can decrease by up to 52.7% [124].

Among the adverse reactions of GLP-1 agonists are described local reactions at the site of administration, such as local erythema, pain and inflammation along with pancreatitis or worsening of renal failure in patients with chronic kidney disease [125].

Dipeptidyl Peptidase-4 is an enzyme that determines the metabolism of GLP-1, decreasing their effectiveness and increasing the glycemic level. Antagonists of this enzyme (such as saxagliptin, alogliptin) mimic the effect of GLP-1 agonist administration by maintaining pancreatic β-cell numbers along with anti-inflammatory and protective effects on overall cardiovascular risk [126,127]. Unlike GLP-1 receptor agonists, adverse reactions are rarer, the rate of hypoglycemia being lower in case of long-term administration, without an increase in body mass index. All of these are burdened by the risk of myocardial remodeling and fibrosis which are accentuated in patients with heart failure [128].

Sodium-glucose cotransporter 2 (SGLT2) is a protein that has the role of reabsorbing glucose that is filtered along with primary urine. Under conditions of

hyperglycemia, SGLT2 is overexpressed in the nephron and hyper-uptake can occur. By blocking this transporter, there is a decrease in the resorption of glucose in the urine and a decrease in blood sugar [129]. In addition to the hypoglycemic effect that canagliflozin, dapagliflozin, empagliflozin have, other effects have been observed, such as the ability to improve the functionality of the cardiovascular system, reduce the rate of chronic kidney disease and normalize the lipid profile of patients [130].

Immunomodulatory treatment in type I DM

In type I diabetes, there is a particular situation, namely autoimmunity, by addressing it the destruction of pancreatic β cells would be reduced, the disease would not progress, and if the onset could be observed it could be prevented [20]. The first immunomodulatory treatment initiated in the case of DM type I was that with cyclosporine, which has a direct inhibitory effect on T cells, which caused a decrease in glycosylated hemoglobin below 7.5%, thus causing remission of the disease after 2 months of continuous treatment [131]. After stopping the treatment, a relapse of the disease occurred, with increased destruction of the remaining β-cells. Although it has the ability to induce disease remission, ciclosporin has significant adverse effects such as nephrotoxicity, the risk of various neoplasms or various allergic reactions. This demonstrated once again the autoimmune component of this pathology and the approach of a new strategy, instead of an intense depression of the immune system, with the aim that the β-cells become accepted and recognized as self, thus having an increased tolerance towards insulin-synthesizing cells [20].

A number of substances have been tried to restore self-tolerance of the immune system in type I diabetes. They have targeted both B cells and T cells, with mediocre results in most cases. Alefacept, a CD+2-targeting monoclonal antibody, was administered for 12 weeks to patients with newly diagnosed type 1 DM compared to placebo, with less C-peptide release but no reduction in the need of insulin, and no decrease in glycosylated hemoglobin [132].

Abatacept is a compound that inhibits T cell activation by interfering with CD80 and CD86 receptors on antigen-presenting cells that can no longer interact with defective T cells and are no longer activated, thus having an early effect on the development of autoimmune cells. Administered for 24 months in patients who had been diagnosed with type I diabetes for less than 1 year, the rate of decrease in pancreatic β-cell counts was similar to that of the control group. Orban et al. concluded that this cause of similar decrease is due to low doses that cannot block antigen-presenting cells or because of alternative pathways of stimulation in the etiology of autoimmune diabetes [133].

Rituximab, an anti-CD20 monoclonal antibody, delayed C-peptide decline by 8.2 months in a cohort of patients with recent-onset type 1 diabetes, but long-term pancreatic β-cell destruction follows its natural course. Thus, 2 years after the onset of C-peptide levels in the group of control patients and those who received monoclonal antibody the results were similar [134].

Another possible solution in the case of type I diabetes is the blocking of some stages of the inflammatory cascade that occurs as a result of the loss of tolerance to pancreatic cells. Administration of canakinumab (an IL-1 blocker) showed no response in reducing C-peptide as a marker of insulin synthesis [135]. Other metabolic pathways that could be altered are those of IL-6 and IL-21. Imatinib is a tyrosine kinase inhibitor used in the treatment of myeloid leukemia. Administered to mice, NOD causes an increase in self-tolerance, with the normalization of blood sugar after 2 weeks of treatment in 80% of cases. Its effects are secondary to inhibition of inflammation through antagonism of platelet-derived growth factor receptors (PDGF-R). In the long term it can lead to prolongation of β-cell life by activating NF-κB and increasing nitric oxide production [136].

Surgical treatment

Metabolic surgery is a new surgical concept in which various organs or systems are manipulated and change their function to achieve a better biological outcome [137]. To this end, a number of interventions have been developed such as duodenal and vague nerve stimulation for type II diabetes, pancreas transplantation or various bariatric surgery procedures with the aim of reducing body weight and the associated metabolic syndrome [138].

Surgical interventions that have demonstrated efficacy in type II diabetes are sleeve gastrectomy, roux-en-y gastric bypass, laparoscopic adjustable gastric bands, and biliopancreatic bypass/duodenal switch, all associated with good results in increasing glycemic control and decreasing substantial weight loss [139].

Standard sleeve gastrectomy is the surgical intervention developed for bariatric surgery in the 2000s, currently being the most well-known and well-researched of all, with good long- and short-term results [140]. The indications for this intervention are represented by morbid obesity with metabolic syndrome, the presence of a liver or kidney transplant and in patients with a body mass index between 30-35 kg/m^2, who have associated comorbidities [141]. The results at 5 years showed that in 58.4% of cases there was a marked decrease in weight [142], and in patients with diabetes associated with obesity, the level of glycosylated hemoglobin decreased from an average from 8.3 to 6.7%, and fasting blood glucose decreased from a mean value of 170.3 to 112.0 mg/dl [143].

Safety studies of sleeve gastrectomy have shown a mortality rate of 0% but a morbidity of 2.2% [144]. The most frequently observed long-term occurrence of

stenoses or strictures but also anastomotic fistula associated with high morbidity, or gastroesophageal reflux disease with an increased risk of Barrett's esophagus (a fact for which the presence of erosive esophagitis before bariatric surgery is a relative contraindication) [145].

Roux-en-Y gastric bypass was first described in 1966 and performed laparoscopically in 1993 [146], being one of the best metabolic interventions to improve hypertension, dyslipidemia, sleep apnea, heart failure and depression [147]. The main indication for this intervention is morbid obesity. In the first months there is a decrease of > 50% which can be maintained in the long term, and in patients with diabetes there is a remission of the disease between 50-80% depending on the duration of the disease and its severity [148]. At an interval of more than 7 years, it was observed that in patients who underwent gastric bypass, the mortality rate from cardiac causes (associated with complications) decreased by 40% in diabetes and cancer [149]. Regarding the rate of perioperative complications, it has been observed that they can be present in 3.5% of cases, along with a mortality between 0.14 and 0.25% [144].

Laparoscopic adjustable gastric banding (LAGB) is the third most common procedure for the relief of morbid obesity and metabolic syndrome [139]. Studies show that it is a simple, effective, reversible and durable procedure if patients are well selected and counseled in the peri-interventional period [150,151]. In studies of 89 patients with morbid obesity and metabolic syndrome, 60 showed improvements at 12 months and 2 years after surgery, with 80 of them at near-normal weight [152]. In patients with diabetes and a high body mass index, a decrease in glycosylated hemoglobin between 1.4 and 2% was observed from the value of 7.9, and the discontinuation of hypoglycemic treatment was reduced from 36.2% before surgery in 12.3% [153].

LAGB is associated with very low mortality and complication rates compared to other bariatric procedures. Perioperative mortality and morbidity rates reached 0.04 for death and 0.9% for morbidity [144]. The possible complications and shortcomings that may appear within this therapeutic approach are represented by the potential of the band to erode the gastric wall, along with its migration or sliding on the gastric wall, esophageal dilatation, all burdened by insufficient weakening [151]. After 15 years after the intervention, it was observed that 29% of the patients had the device intact and its position was the original, while the body mass index was around 35+/-7kg/m^2, with an excellent BAROS score [154].

Biliopancreatic diversion with duodenal switch was first performed laparoscopically in 1999 [155] and is currently the most effective weight loss method [156]. This method has the highest resolution rate of comorbidities associated with excess weight, especially type II diabetes, with cure rates reaching 95% [157]. Indications for the procedure are related to morbid obesity, especially in patients with comorbidities, having the ability to maintain weight within normal limits even after several years [158]. Among the complications that can occur perioperatively, anastomotic fistula, along with pulmonary embolism and respiratory failure, are associated with super-obesity, with death rates between 0-2.7% depending on the technique used, higher rates being for laparoscopic techniques [157], while in 7% of cases reintervention is necessary in the first days [159]. In the long term, the results are satisfactory, only 5% of patients need re-intervention to treat possible metabolic complications. Although it has very good cure rates for type II diabetes, with weight loss and weight maintenance, it is burdened by numerous complications, being reserved only for experienced bariatric surgeons who must monitor the patient throughout life to detect possible subsequent complications [141].

Another alternative to surgical treatment is pancreas transplantation, one of the few treatments that can cure insulin-dependent diabetes, preventing its worsening and associated complications. Simultaneous kidney and pancreas transplantation is the most common form of transplantation in the US, and is most often indicated for those with associated chronic disease. Implantation of a pancreas without kidneys can be performed in patients with acute complications of hyperglycemia, such as ketoacidosis, poor glycemic control with insulin therapy, or in cases where patients cannot achieve their hypoglycemic state at certain times of the day. Renal function must be preserved, as immunosuppressive treatment with calcineurin has nephrotoxic potential [160]. An alternative to total pancreatic transplantation is pancreatic graft transplantation with or without associated renal transplantation, but associated with a high rate of complications such as pancreatic pseudocyst formation and anastomotic or pancreatic fistula [161].

Pancreatic B-cell transplantation is an alternative treatment method that does not require invasive surgical treatment, with moderate efficacy associated with acceptable post-transplant immunosurveillance. Most of the time the cells are infused into the portal vein or under the renal capsule according to the Edmonton protocol [162]. Regarding the results of the pancreas transplant operation, the mortality rate 1 year after the intervention reaches 4%, exceeding 9% in 5 years, in most cases the cause being an acute cardio-vascular event [160].

Comparatively, simultaneous pancreas and kidney transplantation has better survival outcomes than renal transplantation with associated hypoglycemic treatment. Similar results have been observed if only pancreatic transplantation is performed, provided that renal function

is good [163]. Pancreatic graft rejection rate in pancreas transplantation is assessed by calculating insulin requirement and hemoglobin A1c level, so in patients who underwent pancreas transplantation after kidney transplantation, the risk of rejection at 1 year was only 14%, and 44% at 10 years (depending on recipient age, donor age, body mass index and severity of cardiovascular comorbidities) [164].

Following pancreatic transplantation, there was a normalization of carbohydrate metabolism, a decrease in serum lipids and the resumption of normal endothelial function with improvement of neuro and nephropathy, reduction of retinal eye complications but with an increase in the frequency of cataract secondary to treatment with calcineurin inhibitors [160].

Last but not least, diabetic patients with severe complicated peripheral arteriopathy (such as wet gangrene, etc.) may even end up with limb amputations [165].

Psychological treatment

In addition to medical, surgical, dietary treatment, the psychological aspect should not be neglected in the case of patients with diabetes, being able to improve the therapeutic effect of standard treatment methods [166]. By applying cognitive-behavioral therapy, motivational interviewing and patient-centered therapy, better levels of glycosylated hemoglobin were observed in adults with better emotional status. Thus, a concept was developed according to which psychological intervention through specific methods can additionally improve the quality of life of a chronic patient, as well as the level of blood sugar [167].

Cognitive behavioral therapy

Cognitive-behavioral treatment helps patients reorganize their thoughts, dysfunctional beliefs, and change their behavior so that their mental health improves. Since its first use in the treatment of depression, cognitive behavioral therapy has also been developed for various chronic diseases, including diabetes or heart failure [168]. Thus, a manual was developed to change the behavior of the patient with diabetes, giving him tasks that have the ability to change thoughts, negative habits that could aggravate a hyperglycemia, and at the same time help to develop healthy daily routines such as exercise at certain times and a low-carbohydrate diet [169].

Through sustained cognitive behavioral treatment, the effects of persistent hyperglycemia can be modulated, with a decrease in glycosylated hemoglobin levels and a reduction in the risk of general cardiovascular complications in these patients (the effect being felt in both type II and type I patients). Another parameter that was improved by cognitive-behavioral therapy is adherence to the treatment that directly influences the glycemic level, so patients who followed such therapy had better glycemic control and lower rates of giving up the basic treatment (or neglect regimen), compared to those who were not psychologically counseled. The best results were obtained if the treatment period was short, less than 6 weeks, while after this period patients become non-compliant, the mental fatigue and the cost of treatment being the main factors responsible for this response [170].

The interaction between patient and therapist can vary from remote (via a mobile phone or the Internet) to classic face-to-face or group therapy. Among patients with diabetes, good results were seen in patients who were counseled face to face because it was done in a group and the stimulating effect of this method made it more effective [171].

Comparatively, patients with type I diabetes respond better to cognitive behavioral therapy than those with type II diabetes. The first category of consumers of health services are young people. They have a life dependent on insulin therapy and sometimes feel burdened by life-threatening complications, being thus more prone to developing stress related to the disease compared to those with diabetes type II. Thus, psychological treatment in their case is based on acceptance, understanding the disease and developing a lifestyle that can better control the glycemic level [170].

With the onset of diabetes, a series of complications may occur such as chronic pain or bed rest secondary to vascular accidents or amputations, which will lead to high depression and anxiety [172]. Thus, it is necessary that once cognitive-behavioral therapy is initiated, it must also manage or prevent pre-existing psychiatric symptoms. A long-term therapy of more than 6 weeks that also includes a treatment focused on mood disorders improves both glycemic levels and improves or even eliminates anxiety and depression [173].

Through cognitive behavioral treatment, an improvement in patients' weight, cholesterol and HDL-cholesterol was attempted, but no statistical differences were identified between the patient with and without therapy. Only an improvement in the level of serum lipids secondary to weight loss and better glycemic control was noted [174].

Motivational interviewing

One of the best ways in which patients can change some negative aspects of their lives is motivational interviewing [175]. This technique relies on patients' ability to motivate themselves and engage in changing different behaviors by exploring different situations and eliminating uncertainties and hesitations [176]. Thus, in the treatment of chronic diseases such as diabetes, hypertension and obesity, the association of pharmacotherapy with lifestyle changes determined by motivational interviewing proves to be effective. It increases the degree of acceptance of the disease, and

understanding it helps to remove its negative effects through a better ability to reduce the psychological and physical stress associated with the condition [177]. Within this technique, most of the time the psychotherapist has the role of working together with the patient as a partnership, they go together on the path of the disease and when they reach a certain point, the specialist informs the client about the possible options (what else could be done, which are the advantages and disadvantages of the possible methods), the patient being thus helped to solve his problem, but with his own contribution [178].

By applying this method in diabetes, it is possible to achieve decreases in glycosylated hemoglobin along with a reduction in cardiovascular complications of up to 25-35%. It could be a direct consequence, but also secondary to an improved lifestyle with physical activity, a diet rich in vegetables, fruits, lean products with a low intake of processed foods, rich in salt or sugar [179], as well as a better knowledge of the disease through the materials and information provided by the specialist. Similar results were obtained for serum lipid levels [170].

The impact of motivational interviewing was substantial in terms of self-management of the patient with diabetes. Dietary control, exercise and glucose monitoring were better accepted by patients following such therapy than those who were not motivated [180]. The reasons why patients do not comply with the associated diet were represented by not understanding the total calculation of calories consumed, maintaining a fixed meal schedule, what is the relationship between glycemic control and carbohydrate intake, how to get rid of unhealthy habits in the family or how to accept the feeling of hunger. Many of the patients also had problems accepting the need for exercise, integrating it into their lifestyle and work, or not understanding this need. Furthermore, without support from relatives, the exercise program may be initially accepted and later abandoned [181].

Conclusions

Diabetes mellitus is a complex and highly prevalent metabolic disease with significant implications for individuals and health systems worldwide. Its epidemiology is influenced by various factors, including age, genetic predisposition, lifestyle choices, etc. Understanding the pathophysiology of diabetes is crucial for the development of effective treatment strategies. Diabetes management involves a comprehensive approach that includes lifestyle changes, pharmacological interventions, surgical interventions in selected cases as well as psychological support. Ongoing research and advances in medical science aim to improve the prevention, early diagnosis and treatment of diabetes, to significantly improve the quality of life for people affected by the condition.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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