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SCIENCE, CULTURE, SOCIETY – NEW CONTENTS AND EDUCATIONAL CONTEXTS

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What next for diabetes mellitus?

Introduction

Diabetes mellitus is a chronic heterogeneous disease, known for millennia, which essentially afflicts its sufferers until the end of their lives. Although it has already been addressed in numerous scientific publications, its etiopathogenesis is still far from conclusive explanations, and its nature still remains a mystery. Diabetes is currently defined as a group of metabolic diseases characterized by hyperglycemia, that is increased levels of sugar in blood, resulting from impaired synthesis or secretion of insulin released by the β cells of the pancreatic islets of Langerhans. Chronic hyperglycemia leads to the damage, functional disorders and insufficiency of many organs, particularly the eyes, the kidneys, and the cardiovascular system. With regard to its etiology and course, diabetes is divided into type 1, type 2 and gestational type.

The general principle of the contemporary therapy for diabetes involves treating all the coexisting disorders instead of merely restoring the carbohydrate metabolism. The risk of complications of the disease is decreased by such means as normalization of body weight, increased physical activity, balanced diet, treating lipid metabolism disorders accompanying diabetes, as well as arterial hypertension and other cardiovascular diseases, and maintaining the glycemic index at levels possibly closest to its physiological norm.

Symptoms of diabetes mellitus

Characteristic changes occurring in states of uncontrolled diabetes in humans include, among other things, an increase in glucose concentration in blood, intensification of glycogen degradation, and an increase in the rate of gluconeogenesis, the oxidation of fatty acids and the formation of ketone bodies and urea (Drzewoski, 2001). Another indication is a decreased rate of the biosynthesis of glycogen, lipids and proteins in the cells of insulin-dependent tissues, such as muscles and the fatty tissue. These cells use a distinctive, insulin-dependent system of glucose transport

to the protoplasm, whose impairment in diabetes is caused by the high concentration of sugar in blood. Such a transport system is inefficient in the event of insulin deficiency. In the case of insulin-independent cells, the entry of glucose into the cell is largely controlled not by insulin, but by the concentration gradient between its exogenous and endogenous environments. Within such cells, an excessive utilization of glucose might take place. What therefore occurs is the "reversing" of glucose from insulin-dependent metabolic pathways to those which do not require the presence of the said hormone. An excessive utilization of glucose, resulting from an increase in its intracellular concentration and affecting the course of many processes within insulin-independent tissues, might contribute to many pathological changes in the course of chronic diabetes (Busetto et al., 2016).

In the course of diabetes mellitus, there are numerous factors leading to the increased production of free radicals, while at the same time impairing the potential for their elimination. Oxidative stress contributes primarily to the modification of protein and DNA structure, which is negative for the organism (Liu et al., 2016), as well as to deficiencies in NADPH oxidase which is crucial for both the production and action of such antioxidants as glutathione or vitamin C (Niki, 1991). Free radicals in diabetes are also formed as a result of the non-enzymatic glycosylation of proteins, which in turn is a consequence of chronic hyperglycemia. Non-enzymatic glycation of proteins is a process occurring spontaneously in living organisms and the accumulation of its products in tissues intensifies with age (Yamagishi, Matsui, 2016), which might indicate that non-enzymatic glycosylation contributes to the process of aging of the organism. At the same time, such diseases as diabetes mellitus or renal insufficiency lead to the intensification of non-enzymatic glycosylation.

An increase in the non-enzymatic glycation of proteins can be observed in uncontrolled or improperly controlled diabetes. In the human organism, the γ-amino groups of lysine and the free amino groups of valine in protein chains undergo a three-stage glycation reaction. A glucose molecule is bonded to a protein, which might cause significant changes in its properties. The glycation process depends on the concentration of glucose and the duration of the process. In chronic diabetes, the glycosylated form of e.g. hemoglobin (HbA1c) has a different affinity for oxygen, which may contribute to hypoxia. Additionally, in chronic diabetes, glucosamine-protein complexes are formed which cause biochemical and morphological changes in capillaries. Also, the glycosylation of collagen increases, which affects the thickening of the glomerular basement membrane of the kidney (Frei et al., 1988). The intensified transformation of glucose into fructose on the polyol pathway in diabetes results from an increased intracellular concentration of glucose in tissues using an insulin-independent transport system (the lens, the liver, the kidneys, peripheral nerves) and from a high NADPH/NADP+ ratio caused by a decreased rate of other reduction reactions, e.g. fatty acid synthesis. It is worth mentioning that the accumulation of sorbitol leads to osmotic disorders, which play a significant role in the etiology of cataract (Mehta et al., 2006).

Chronic diabetes might lead to numerous complications. Some of them are affected by the buildup of cholesterol in arteries, atherosclerosis of coronary vessels or large blood vessels of the lower limbs. Impairments of the nervous system, including the autonomic nervous system, may also occur. Moreover, the eyes and the kidneys might be subjected to characteristic alterations due to changes in the lens and in the basement membrane of small blood vessels. In this context, diabetes mellitus is also interpreted as the most common cause of end-stage renal disease, which results from damage to glomerular capillaries constituting a part of the general microangiopathy (Morita et al., 1991). The risk of development of those complications is much higher when diabetes is improperly monitored. It is not a rule, though, as they might also develop chronically in patients receiving adequate treatment (Chan et al., 2016).

Insulin and glucagon

Insulin and glucagon control the metabolism of peripheral tissues and take part in maintaining their homeostasis (Ochwanowska et al., 2009; Witek et al., 2001). Insulin is an anabolic hormone which induces the biosynthesis of proteins, fats and glycogen, and at the same time inhibits the degradation of those compounds. The liver, muscles and fatty tissue are areas which are particularly rich in insulin receptors (Cariou, 2015). Glucagon affects the increase in catabolic processes, mainly in the liver (Authier et al., 1992). A normal concentration of glucose in plasma secures the main source of energy for tissues and its utilization requires a constant presence of insulin. Thanks to the antagonistic effects of glucagon and insulin, the organism is protected from the development of hypoglycemia during hunger or intensive physical exercise, that is in cases when a mobilization of greater sources of glucose is necessary (Nathan, 2015). It is understandable that insulin deficiency impairs the utilization of glucose and the excess of glucagon increases its concentration in blood (Gallichan, 1997). A high concentration of glucagon as compared to insulin in diabetic patients considerably accelerates the breakdown of glycogen and stimulates the excessive rate of the release of liver glucose into the blood. As a result of diabetes, a significant qualitative change of energy substrates may occur, particularly from carbohydrates to fats, which – due to the formation of ketone bodies – might lead to acidosis, coma, or even death, if diabetic patients do not receive adequate treatment. The consequence of diabetes is a long-term emaciation of the organism.

Regulation of the secretion of insulin and glucagon

Factors regulating the secretion of insulin and glucagon and inducing changes in their concentration in the circulating blood include the normal concentration of glucose and amino acids in plasma, the presence of many types of hormones, as well as sympathetic and parasympathetic stimulation. In the presence of insulin, amino acids can increase the rate of entry into cells and prevent the occurrence

of hypoglycemia through adequate stimulation of glucagon secretion (Battezzati et al., 2003).

The concentration of glucose in blood depends on the speed of its absorption in the intestines, the rate of its storage in the liver and the degree of its utilization by peripheral tissues. The most important parameter for the diagnosis of diabetes is thus the concentration of glucose in blood primarily in fasted patients. Normal concentration of glucose in fasting blood oscillates in the range of 70–105 mg/dL (3.89–5.83 mmol/L); after a meal it might increase to 126 mg/dL (7.0 mmol/L). Glucose concentration of over 180 mg/dL (10.0 mmol/L) induces glucosuria. According to guidelines developed by the National Institutes of Health (NIH), an agency of the United States government dealing with biomedical and public health research, in order to diagnose diabetes, the concentration of sugar in fasting blood should be higher than 140 mg% (100 mg% = 5.6 mmol/L sugar in blood), that is 7.84 mmol/L. This or higher value should be verified at least twice (Sharabi, 2015). If the results do not allow for a definite interpretation, the oral glucose tolerance test (OGTT) should be performed. A patient receives 75 g of glucose and the determination of glucose concentration in blood is carried out at 30-minute intervals for 2 hours after its administration. In healthy individuals, the concentration 2 hours after the oral load of glucose is either the same, similar or lower than the initial concentration. Diabetes is diagnosed when the concentration of glucose in venous blood plasma 2 hours after the load of this sugar is higher than 10.0 mmol/L.

Glucose tolerance lowers with age, which is why it is recommended that an adjustment should be made to the values of glucose in whole blood or plasma by adding 0.056 mmol/L per each year over 60 years of life. Negative effects of diabetes, irrespective of its pathogenesis and type, are primarily the consequence of hyperglycemia and pertain mainly to the vascular system. The effects of those changes are retinopathy, nephropathy, or diabetic neuropathy (Gerich, 2000). The etiology of vascular complications of diabetes has yet to be fully determined, even though the correlation between hyperglycemia and vascular disorders is evident. It has been demonstrated that an adequate management of glycemia allows for a more detailed analysis of the development of complications with respect to vascular diseases (Van Leiden et al., 2003).

Research on diabetes – historical outline

It is known that man has been plagued by diabetes for centuries, for the Ebers Papyrus from as early as 1550 BC mentions a disease whose course was accompanied by polyuria. Hippocrates observed that fly swarms tended to fly towards the urine of those individuals whose secretion was sweet and whose disease, through the state of coma, caused immediate death. In the 2nd century AD, Aretaeus of Cappadocia characterized the condition as “the dissolution of body and extremities in urine”. The description referred to the excretion of large amounts of urine (polyuria) and decreased body weight in patients – symptoms characteristic for

uncontrolled diabetes. Because of the "unquenchable thirst" accompanying the condition, Aretaeus termed it diabetes (Greek *diabetes* – siphon). The second element of the name, i.e. mellitus, was not added until the 18th century, upon determining that the urine of diabetic patients had a sweet taste (Latin *mellitus* – sweet) (Ionescu-Tirgoviste, 1996; Majumdar, 2001). The main contemporary stream of research began in 1886, when Josef von Mering, a German scholar, discovered the so-called phlorizin diabetes in dogs.

Diabetes is the most common endocrine disorder connected with endocrine pancreatic insufficiency. In 1921, Frederick Grant Banting, a Canadian medical scientist, and Charles Herbert Best, an American-Canadian biochemist, extracted insulin from canine pancreatic islets and found that the extract decreased the concentration of glucose in blood (Cheymol, 1971; Witek, Kołątaj, 2012). The discovery would not, however, be possible if it was not for the earlier research studies conducted by Oskar Minkowski, a German doctor. Minkowski proved that there existed a connection between diabetes mellitus and the pancreas, and that it was precisely that organ where the cause of the disease should be sought. In order to demonstrate that the human organism was unable to function without the pancreas, he carried out scientific experiments on dogs with the help of Joseph von Mering, the co-discoverer of diabetes. In 1889, they found that complete pancreatectomy (complete removal of the pancreas) in dogs resulted in symptoms similar to diabetes mellitus in humans (von Mering, Minkowski, 1890). Since then, research has developed on the pancreas as a source of medicinal substance which could be used for treating diabetes. In partial atrophy of the organ, after excretory duct ligation, the undamaged Langerhans islets were still able to protect the organism from the disease.

The discovery of pancreas-derived diabetes by Minkowski and von Mering triggered a worldwide search for an antidiabetic agent within the pancreatic gland (von Mering, Minkowski, 1890). At the beginning of the 20th century, patients suffering from diabetes were diagnosed with the presence of pathological cells in the pancreatic islets (Dominguez, Licata, 2001; Hara et al., 2016). For that discovery, and for "obtaining insulin in the form of an active extract from animal pancreas and its application in the treatment of diabetes", the Nobel Prize in Physiology or Medicine was awarded jointly to Frederick Banting and John James Rickard Macleod, a Scottish physiologist, in 1923 (Bliss, 1989; Shampoo, Kyle, 2005). Since then, the application of insulin revolutionized the treatment of diabetes and became the ground for the worldwide research into the structure and function of insulin. A major advancement was reached in 1955, when Frederick Sanger, a British biochemist, published his report on the primary structure of insulin, constituting the first representation of the sequence of amino acids in a peptide hormone molecule (Maruyama, 2002). In 1969, Dorothy Mary Hodgkin, a British biochemist, determined the spatial structure of insulin based on crystallographic studies (Howard, 2003).

Types of diabetes

Diabetes belongs to a group of conditions described as civilization diseases and its prevalence in the human population has reached alarming levels in the past few years (Aziz et al., 2015). The World Health Organization has deemed diabetes to be the epidemic of the 20th (now also 21st) century. It is estimated that the problem is now being faced by a population of approximately 200 million people, and the number is predicted to reach over 300 million by 2025 (WHO, 1994).

Today, it is known that two main types of diabetes – type 1 and type 2 – impair the metabolism of not only carbohydrates, but also proteins and fats, and that the disorders very often appear long before the actual manifestation of the disease (Polsky, Ellis, 2015).

Diabetes mellitus type 1

Diabetes type 1 occurs mostly in children and adolescents. It is diagnosed in about 0.25% of individuals under 20 years of age, which is why the type has been termed as juvenile diabetes or IDDM (insulin-dependent diabetes mellitus). This type of diabetes is completely insulin-dependent, which means that pancreatic β cells in diabetic patients release very little or no insulin at all. Diabetes type 1 of autoimmune character, also called LADA (latent autoimmune diabetes in adults), can have a slow onset and occur in adults. It is characteristic of 50% of patients of slim build and older age – an age group typical of diabetes type 2 (Pozzilli, Di Mario, 2001). The underlying cause of diabetes type 1 is the autoimmune destruction of β cells within the Langerhans islets. Predisposition to this type of diabetes is genetic and may occur at any age of life. Environmental factors, such as diet, stress or viral infections, also play a significant role in the development of diabetes type 1.

Autoimmune processes are believed to be the cause of diabetes type 1 (Collessa et al., 2002; Körner et al., 2002). A significant role in its pathogenesis is also played by viral factors, which can be inferred from the increased prevalence of type 1 diabetes after rosacea or Coxsackie virus infections (Trukhan, 2001), less often after mumps or cytomegaly. This type of diabetes can also be transmitted as a result of bone marrow transplantation or experimental tests. The autoimmune process involves the destruction of overloaded β cells of Langerhans islets. A destruction of 75% of their number results in the impairment of glucose tolerance and induces the first symptoms of the disease (Peczyńska et al., 2002).

Despite research studies that have been carried out, inter alia, on twins, no sufficient explanation has been found of whether genetic predispositions have any influence on the occurrence of type 1 diabetes, even thou there exists data validating such possibility. Clinicists have been searching for similarities in the structure and function of specific types of antibodies in parents, their children and siblings suffering from diabetes type 1 (Bieniasz, Wąsikowa, 2002). In 10% of children with diabetes type 1, the disease was diagnosed in one of the parents, and only 5% of those children had usually one grandparent with this type of diabetes. If both

parents are diabetic, the risk of inheriting the disease by each of their children is 10%, while if one of the siblings has diabetes type 1, the risk for it in another one is 3–7%. In twins, the risk for developing the disease in the other sibling is 20–30%, while in monozygotic twins the risk is 30–50%.

Studies by Kubryn et al. (2002) found that main genes connected with the predisposition to diabetes mellitus type 1 in the Polish population are the HLA-DRB1 and DQB1 genes. Krischer et al. (2003) have continued research into the strategy of searching for immune markers in the relatives of patients with diabetes type 1.

Research on diabetes mellitus type 1

The issue of diabetes prevention constitutes a challenge for diabetologists and research into the matter is being carried out constantly. As regards the pathogenesis of diabetes type 1, particular emphasis is being placed on the role of oxidative stress, and the possibility is being explored of the application of "sweepers" of oxygen free radicals, e.g. nicotinamide or vitamins C and E (Crino et al., 2002). However, the European Nicotinamide Diabetes Intervention Trial (ENDIT), a large multinational study on the role of nicotinic acid concluded in 2002, did not verify that it had any significant protective value.

High hopes were also placed on the preventive administration of small doses of insulin to children presumed to be at high risk for diabetes type 1. However, studies on the parenteral administration of insulin did not yield any clear proof that the procedure indeed prevented the development of the disease (Pozzilla, 2002). What is more, no conclusive reports have been presented concerning the application of anti-inflammatory preparations or vitamin D3 analogs in the regulation of the concentration of ionized calcium which has a significant impact on insulin secretion. However, research papers have been published reporting the existence of a strong effect of vitamin D3 on the inhibition of diabetes type 1 through modulating the activity of T cells and reducing the speed of the insulinitis process (Zella, DeLuca, 2003).

It is indicated that a positive effect on the normal functioning of pancreatic β cells might be produced by natural breastfeeding and a several-month period of gluten-free diet, which is believed to prevent the immunotoxic effect of cow's milk protein (Pastore et al., 2003). Additionally, attempts are being made at the immunosuppression and immunomodulation of autoimmunization processes and the acceleration of β cell apoptosis by means of gene therapy in both the treatment and prevention of this type of diabetes (Efrat, 2002; Falqui et al., 2001).

Diabetes mellitus type 2

Diabetes type 2 is referred to as adult-onset diabetes or NIDDM (non-insulin--dependent diabetes mellitus). It is connected with genetic predispositions of a given human ethnic group and with dietary habits, and is mostly precipitated by poor physical activity, obesity and advanced age. Individuals with diabetes type 2

requiring insulin treatment are not in fact insulin-dependent, as their organisms are still capable of the residual secretion of the hormone.

Diabetes mellitus type 2 is the most common type of diabetes and is characterized by a dichotomy of sorts. The condition is genetically-based but is also considerably affected by environmental factors inducing this genetic predisposition. The genetic and the environmental factors have an equal share in increasing or inhibiting the rate of insulin secretion.

It seems that researchers should pay special attention to the crucial role of genes responsible for the structure of glucose transport proteins and the regulators of their activity, including protein kinase C, phospholipase and the phosphatidylinositol system, though the multigenic pathogenesis of diabetes type 2 requires a further in-depth analysis. A significant role in the regulation of insulin secretion can also be played by changes within mitochondrial DNA or the genes of certain regulatory proteins (Fajans et al., 2001). An impairment of insulin secretion may be caused by different types of polymorphism within the genes of glucose transport proteins, specific glycolytic pathway enzymes, potassium channel proteins and the related sulphonylurea receptors, as well as calcium channel proteins and the so-called calcium cascade proteins (Malaisse, 2001). Different types of polymorphism can lead to reducing the rate of insulin secretion and increasing the amount of damage to pancreatic β cells, especially in the case of obesity-related insulin resistance.

Environmental factors are essentially elements of the contemporary lifestyle of developed civilizations, particularly high-calorie foods combined with very little physical activity, constituting the main cause of obesity and the associated insulin resistance (Putti et al., 2016). Metabolic disorders related to obesity, such as hypertriglyceridemia, low HDL levels (American Diabetes Association, 2003), hyperinsulinemia or impaired glucose tolerance, are the first symptoms of a developing polymetabolic syndrome (Taylor et al., 2015).

Research on diabetes mellitus type 2

Diabetes type 2 is a progressive condition characterized by the initial development of insulin resistance along with an insulin secretion defect, and then the prevalent impairment of β cell functions with persistent insulin resistance (WHO, 1999). The European Diabetes Policy Group (EDPG) provided guidelines clearly indicating the need to adjust the treatment regimen to the stage of diabetes mellitus. According to EDPG recommendations (EDPG, 1999), treatment should begin with the modification of lifestyle and dietary patterns. However, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that this method does not help to achieve, for instance, a significant reduction of the level of glycated hemoglobin, that is glycemia (UKPDS, 1998). EDPG recommends to begin with monotherapy, and in the next step switch to combination therapy with two, or even three hypoglycemic drugs with different action mechanisms. Nevertheless, further preventive treatment should allow for the need to introduce insulin therapy. It has been found that in the

period of 5 years of the duration of diabetes type 2, the inefficiency of sulphonylurea derivatives occurs in about 1/3 cases. The first stage of insulin treatment of this type of diabetes should consist of the so-called combination therapy, i.e. using both oral medications and insulin (Yki-Jarvinen, 2001), while the next stage should involve a complete substitution by insulin, through various models of use of pre-mixed insulin, or monotherapy, e.g. a basal-bolus regimen – a form of intensive insulin therapy.

The treatment regimen for diabetes type 2 should be monitored and changed as soon as the effectiveness of the originally adopted solutions becomes limited. Such an approach allows to fulfil criteria for regulating this type of diabetes, which are not limited to carbohydrate balance, but cover the normalization of lipid disorders and the regulation of arterial hypertension as well (Lamos et al., 2016).

Other types of diabetes mellitus have also been differentiated. Gestational diabetes develops in 3% of pregnant women, while MODY diabetes, that is maturity onset diabetes of the young, occurs in less than 2% of the population of type 2 diabetic patients. There exists convincing evidence that the pathogenesis of diabetes type 2 and its commonly coexisting disorders are a consequence of the interaction between genetic and environmental factors (Hitsumoto, 2016).

What next for diabetes? Future prospects

Since the central problem in diabetes mellitus is the impaired functioning of the pancreas, it seems that the easiest solution would be to replace the impaired organ. Pancreas transplantation has been known since 1966, when the first such surgery was performed in the USA. In Poland, pancreas transplants have been carried out since 1988. The surgery has been performed on patients with diabetes type 1. Apart from living organ transplantation, research studies have also been carried out into a synthetic substitute for pancreas. The first such prototypes were created in the 70s of the 20th century, but they were rather large. Modern models are much smaller, but they are still unfit for everyday use. Nonetheless, researchers entertain the hope that the endeavor will prove successful. A method less invasive than the transplantation of the whole pancreas is transplanting the Langerhans islets. This procedure, however, is still in the phase of experimentation. The problem is that the cells are transplanted from a deceased donor, which is why their number from a single donor is too low, and their functional properties decline during the transplantation procedure. Another disadvantage is the fact, that each transplant entails the need for a lifelong immunosuppressive therapy, which reduces the efficacy of the immune system and weakens the organism.

An interesting solution for the transplantation-based treatment of diabetes is stem cell transplant. Stem cells, which are obtained from cord blood and peripheral blood, can develop into pancreatic β cells responsible for the synthesis of insulin. Such transplantations have been successfully performed in Poland and in Brazil. So far, the method has been used in the treatment of diabetes type 1.

People suffering from diabetes mellitus very often have difficulties maintaining a healthy weight. Therefore, a good method in the treatment of diabetes seems to be any measure adopted against obesity. One of those methods is treatment with the use of the Tantalus II generator. Three pairs of electrodes are laparoscopically implanted into the patient's stomach walls. The electrodes are connected to an electrical impulse generator located under the skin, similarly to a pacemaker. Unlike a pacemaker, however, the Tantalus II generator is not continuously active in an obese patient, but creates an impulse when detecting that food is being delivered into the stomach. The impulse increases the number and intensity of gastrospasms, which in turn increases the speed of gastric emptying. This is of particular importance, as diabetic patients suffer from delayed gastric emptying. But this is not where the task of the generator ends. The electrical impulse reaches the satiety center of the brain through the vagus nerve, triggering a signal informing the organism about reaching satiety. It seems that treatment using the Tantalus II system might change the lives of those type 2 diabetes patients in which neither diet, nor physical exercise bring any desired outcomes in terms of blood sugar regulation. Observations of patients treated with the use of the Tantalus II generator suggest, that the system provides an efficient and very promising treatment method, which prevents damage to the cardiovascular system, the kidney or the eyes, and – most importantly – relieves sufferers from the need to take insulin (Sanmiguel et al., 2009). Still, there are certain medical contraindications to this treatment method, including, among other things, diabetes type 1, insulin therapy, diabetes lasting more than 10 years, and the age of over 65 years.

Perhaps the next step in the fight against diabetes mellitus type 2 might be the use of gliflozin drugs – sodium-dependent glucose cotransporter 2 inhibitors. They are a class of orally administered medications used in the treatment of diabetes type 2. Gliflozin drugs are expressed in the kidneys, inducing an increased excretion of glucose in urine. This contributes to reducing the level of glucose in blood, burning extra calories, and consequently reducing body weight (Doggrell, Tuli, 2014). The medication is relatively new; therefore, its adverse effects have not been fully explored yet.

Perhaps a new direction of search for diabetes medications might be an attempt to increase the storage of glucose in the liver. Throughout the last decade, the most significant advancement in the treatment of diabetes type 2 was connected with the development of incretin-based drugs which control glucose homeostasis by affecting the intestinal-pancreatic axis and its central figure, namely the glucagon--like peptide-1 (GLP-1). GLP-1 analogs are parenterally administered drugs acting directly on pancreatic β cells, stimulating them to secrete insulin only as glycemia increases. They do not act under conditions of normoglycemia, and as such do not trigger hypoglycemia (Jafri et al., 2016).

Researchers of different specialties indicate novel and promising directions in the fight against not only diabetes mellitus, but also autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis or celiac disease. Many of the medications

tested so far have not yielded the desired improvement in the treatment of the above and other conditions. Today, diabetes mellitus is sadly still not a curable disease, although by virtue of the progressive achievements of researchers within many interdisciplinary fields, the disease is becoming less and less burdensome, and the risk of complications, which are undoubtedly an additional source of worry, continues to decrease.

References

Ajanki T., 2003, *Nobel Prize for discovery of insulin but several scientists wanted to share the honor*, Lakartidningen, 100, 3428–3429.

American Diabetes Association, 2003, *Management of dyslipidemia in adults with diabetes*, Diabetes Care, 26, 82–96.

Authier F., Desbuquois B., de Gallé B., 1992, *Ligand-mediated internalization of glucagon receptors in intact rat liver*, Endocrinology, 131, 447–457.

Aziz Z., Absetz P., Oldroyd J., Pronk N.P., Oldenburg B., 2015, *A systematic review of real-world diabetes prevention programs: learnings from the last 15 years*, Implementation Science, 15, 172–176.

Battezzati A., Benedini S., Fattorini A., Losa M., Mortini P., Bertoli S., Lanzi R., Testolin G., Biolo G., Luzi L., 2003, *Insulin action on protein metabolism in acromegalic patients*, American Journal of Physiology. Endocrinology and Metabolism, 284, E823–E829.

Bieniasz J., Wąsikowa R.B., 2002, *Incidence of diabetes and immunological risk factor in families of children and adolescents with type 1 diabetes*, Journal of Pediatric Endocrinology and Metabolism, 15, 1073–1075.

Bliss M.J.J.R., 1989, *Macleod and the discovery of insulin*, Quarterly Journal of Experimental Physiology, 74, 87–96.

Busetto L., Luijkx K.G., Elissen A.M., Vrijhoef H.J., 2016, *Context, mechanisms and outcomes of integrated care for diabetes mellitus type 2: a systematic review*, BMC Health Services Research, 15, 18–22.

Cariou B., 2015, *Pleiotropic effects of insulin and GLP-1 receptor agonists: Potential benefits of the association*, Diabetes and Metabolism, 41, 6S28–6S35.

Chan C.M., Chim T.M., Leung K.C., Tong C.H., Wong T.F., Leung G.K., 2016, *Simultaneous pancreas and kidney transplantation as the standard surgical treatment for diabetes mellitus patients with end-stage renal disease*, Hong Kong Medical Journal, 22, 62–69.

Cheymol J., 1971, *Discovery of insulin by Banting and Best, 50 years ago*, Bulletin de Academie Nationale Medicine, 155, 836–852.

Collessa M., Minicucci L., Testa M., 2002, *Relationship between celiac disease, type 1 diabetes and other autoimmune diseases*, Journal of Pediatric Endocrinology and Metabolism, 15, 1075–1077.

Crino A., Achiaffini R., Ciampalini P., 2002, *Residual beta-cell function two years after diagnosis of type 1 diabetes: effects of intensive insulin therapy and nicotinamide*, Journal of Pediatric Endocrinology and Metabolism, 15, 1076–1078.

Doggrell S.A., Tuli R., 2014, *Dapagliflozin – do we need it registered for type 2 diabetes?*, Expert Opinion in Pharmacotherapy, 15, 1631–1635.

Dominguez L.J., Licata G., 2001, *The discovery of insulin: what really happened 80 years ago*, Annali Italiani di Medicina Interna, 16, 155–162.

Drzewoski J., 2001, *Cukrzyca typu 2 – wybrane zagadnienia z patofizjologii, diagnostyki i leczenia*, A-Medica Press, Bielsko Biała, 65–80.

EDPG, 1999, *European Diabetes Policy Group 1998–1999. Podręczny poradnik postępowania w cukrzycy typu 2*, Medycyna Praktyczna, 10–20.

Efrat S., 2002, *Preventing type 1 diabetes mellitus: the promise of gene therapy*, American Journal of Pharmacogenomics, 2, 129–134.

Fajans S.S., Bell G.I., 2001, *Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young*, New England Journal of Medicine, 345, 971–980.

Falqui L., Calebiro D., Berselli P., 2001, *Insulin-gene therapy for type 1 diabetes*, Journal of Pediatric Endocrinology and Metabolism, 14, 1028–1033.

Frei B., Stocker R., Ames B.N., 1988, *Antioxidant defence and lipid peroxidation in human blood plasma*, Proceedings of the National Academy of Sciences, 85, 9748–9752.

Gallichan M., 1997, *Self-monitoring of glucose by people with diabetes: evidence based practice*, British Medical Journal, 314, 964.

Gerich J.E., 2000, *Physiology of glucose homeostasis*, Diabetes, Obesity and Metabolism, 2, 345–350.

Hitsumoto T., 2015, *Factors Associated with High-sensitivity Cardiac Troponin T in Patients with Type 2 Diabetes Mellitus*, Journal of Nippon Medical School, 82, 274–280.

Howard J.A., 2003, *Dorothy Hodgkin and her contributions to chemistry*, Nature Reviews Molecular Cell Biology, 4, 891–896.

Ionescu-Tirgoviste C., 1996, *Insulin, the molecule of the century*, Archives of Physiology and Biochemistry, 104, 807–813.

Jafri L., Saleem S., Calderwood D., Gillespie A., Mirza B., Green B.D., 2016, *Naturally-occurring TGR5 agonists modulating glucagon-like peptide-1 biosynthesis and secretion*, Peptides, doi: 10.1016/j.peptides.2016.01.015.

Körner A., Arato A., Medaecsy L., Rideg O., 2002, *Increased risk of other autoimmune disorders in children with type 1 diabetes mellitus*, Journal of Pediatric Endocrinology and Metabolism, 15, 1064–1066.

Krischer J.P., Cuthbertson D.D., Yu L., Orban T., Maclaren N., Jackson R., Winter W.E., Schatz D.A., Palmer J.P., Eisenbarth G.S., 2003, *Screening for the identification of multiple antibody-positive relatives of individuals with type 1 diabetes*, Journal of Clinical Endocrinology and Metabolism, 88, 103–108.

Kubryn I., Młynarski W., Trippenbach-Dulska H., 2002, *Związek genów HLA-DRB1, DQA1 i DQB1 z rodzinnym występowaniem cukrzycy typu 1. Badania wieloośrodkowe*, Choroby Przemiany Materii Wieku Rozwojowego, 8, 25–28.

Lamos E.M., Levitt D.L., Munir K.M., 2016, *A review of dopamine agonist therapy in type 2 diabetes and effects on cardio-metabolic parameter*, Prim Care Diabetes, 10, 60–65.

Liu X., Gan W., Zou Y., Yang B., Su Z., Deng J., Wang L., Cai J., 2016, *Elevated Levels of Urinary Markers of Oxidative DNA and RNA Damage in Type 2 Diabetes with Complications*, Oxidative Medicine and Cellular Longevity, doi: 10.1155/2016/4323198.

Majumdar S.K., 2001, *Glimpses of the history of insulin*, Bulletin Indian Institute History of Medicine (Hyderabad), 31, 57–70.

Malaisse W.J., 2001, *On the track to the beta-cell*, Diabetologia, 44, 393–406.

Maruyama K., 2002, *Frederick Sanger, the pioneer of the sequence determination of protein and Nucleic acids*, Tanpakushitsu Kakusan Koso, 47, 1312–1322.

Mehta J.L., Rasouli N., Sinha A.K., Molavi B., 2006, *Oxidative stress in diabetes: A mechanistic overview of its effects on atherogenesis and myocardial dysfunction*, International Journal of Biochemistry and Cell Biology, 38, 794–803.

Nathan D.M., 2015, *Diabetes: Advances in Diagnosis and Treatment*, JAMA, 8, 1052–1062.

Niki E., 1991, *Acytion of ascorbic acid as a scavenger of active and stable oxygen radicals*, American Journal of Clinical Nutrition, 54, 11195–111245.

Ochwanowska E., Witek B., Kołątaj A., 2009, *The effect of intraperitoneally administered glucagon on the lysosomal enzyme activity in the liver of the mice*, Animal Science Papers and Reports, 27(4), 371–375.

Pastore M.R., Bezziagaluppi E., Belloni C., 2003, *Six months of gluten-free diet do not influence autoantibody titers, but improve insulin secretion in subjects at high risk for type 1 diabetes*, Journal of Clinical Endocrinology and Metabolism, 88, 162–165.

Peczyńska J., Urban M., Głowińska B., Florys B., 2002, *Prevalence of thyroid diseases in children and adolescents with diabetes type 1*, Pediatric Endocrinology, 53, 174–175.

Polsky S., Ellis S.L., 2015, *Obesity, insulin resistance, and type 1 diabetes mellitus*, Current Opinion in Endocrinology, Diabetes and Obesity, 22, 277–282.

Pozzilli P., 2002, *The DPT-1 trial: a negative result with lessons for future type 1 diabetes prevention*, Diabetes Metabolism Research and Reviews, 18, 257–259.

Pozzilli P., Di Mario U., 2001, *Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult). Definition, characterization, and potential prevention*, Diabetes Care, 24, 1460–1467.

Putti R., Migliaccio V., Sica R., Lionetti L., 2016, *Skeletal Muscle Mitochondrial Bioenergetics and Morphology in High Fat Diet Induced Obesity and Insulin Resistance: Focus on Dietary Fat Source*, Front in Physiology, 20, 426–429.

Sanmiguel C.P., Conklin J.L., Cunneen S.A., Barnett P., Phillips E.H., Kipnes M., Pilcher J., Soffer E.E., 2009, *Gastric electrical stimulation with the TANTALUS System in obese type 2 diabetes patients: effect on weight and glycemic control*, Journal of Diabetes Science and Technology, 1, 964–970.

Shampoo M.A., Kyle R.A., 2005, *Frederick Banting – Nobel laureate for discovery of insulin*, Mayo Clinic Proceedings, 80, 576–579.

Sharabi K., Tavares C.D., Rines A.K., Puigserver P., 2015, *Molecular pathophysiology of hepatic glucose production*, Molecular Aspects of Medicine, 46, 21–33.

Tamura Y., Araki A., 2015, *Diabetes mellitus and white matter hyperintensity*, Geriatrics and Gerontology International, 1, 34–42.

Taylor S.R., Meadowcraft L.M., Williamson B., 2015, *Prevalence, Pathophysiology, and Management of Androgen Deficiency in Men with Metabolic Syndrome, Type 2 Diabetes Mellitus, or Both*, Pharmacotherapy, 35, 780–792.

Trukhan D.I., 2001, *Anti-Coxsakie B viruses humoral immunity status in patients with pancreatic diseases*, Voprosy Virusologii, 46, 33–36.

UKPDS, 1998, *United Kingdom Prospective Diabetes Study Group: Intensive blood-glucose control with sulfonylurea or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes*, Lancet, 352–837.

Van Leiden H.A., Dekker J.M., Moll A.C., Nijpels G., Heine R.J., Bouter L.M., Stehouwer C.D.A., Polak B.C.P., 2003, *Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study*, Archives of Ophthalmology, 121, 245–251.

Von Mehring J., Minkowski O., 1890, *Diabetes mellitus nach Pankreasextirpation*, Archiv of Experimental Pathology and Pharmacology, Leipzig, 26, 371–379.

WHO, 1994, *World Health Organization*. *Prevention of diabetes mellitus. Technical Report Series No 844*, WHO, Geneva.

WHO, 1999, *Definition, diagnosis and classification of diabetes mellitus and its complications*, WHO, Geneva.

Witek B., Kołątaj A., 2012, *Z historią w tle o glukozie, erytrocycie i ubikwitynie*…, Wydawnictwo Naukowe SGGW, Warszawa, 1–250.

Witek B., Król T., Kołątaj A., Ochwanowska E., Stanisławska I., Ślewa A., 2001, *The insulin, glucose and cholesterol level and activity of lysosomal enzymes in the course of the model alloxan diabetes*, Neuroendocrinology Letters, 22(4), 240–244.

Yamagishi S.I., Matsui T., 2016, *Protective role of sulphoraphane against vascular complications in diabetes*, Pharmaceutical Biology, 3, 1–11.

Yki-Jarvinen H., 2001, *Combination therapies with insulin in type 2 diabetes*, Diabetes Care, 24, 758–763.

Zella J.B., DeLuca H.F., 2003, *Vitamin D and autoimmune diabetes*, Journal of Cell Biochemistry, 88, 216–222.

What next for diabetes mellitus?

Abstract

Diabetes mellitus is a metabolic disease, characterized by an increased concentration of glucose in blood, accompanied by disordered metabolism of carbohydrates, fats and proteins resulting from insufficient secretion or action of insulin. Diabetes is a chronic disease which generally afflicts its sufferers until the end of their lives. The continuous progress in the treatment and, above all, prevention of diabetes has become a significant factor which might contribute to reducing the incidence of different groups of concurrent complications. The manifold aspects of the significance of diabetes as a problem, which is not solely of a metabolic nature, inclines researchers to adopt an interdisciplinary approach to the disease. The multifactorial and comprehensive prevention and treatment of diabetes through, among other things, adequate pharmacological intervention, might significantly reduce the risk for its numerous multi-organ complications, but also the risk of patient's death.

Key words: diabetes, insulin, glucagon

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