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From Diagnosis to Lifestyle The Impact of Sports on MODY Diabetes Management

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Abstract

Introduction and objectives: Diabetes is a group of diseases that is currently estimated to affect approximately 537 million adults worldwide. Diabetes can develop due to many factors, including autoimmunity, genetics and insulin resistance. The presented article will discuss the type of monogenic diabetes - maturity onset diabetes in young. This is a relatively rare form of diabetes, affecting no more than 5% of patients with the disease, but it is important to correctly differentiate it and implement appropriate therapy to prevent the development of complications. In addition, the article discusses a group of antidiabetic drugs - sulfonylurea derivatives, which are widely used in diabetic patients.

Review and methods: Review and summary of studies and scientific articles avaliable in open-source format on Google Scholar and PubMed.

Abbreviated description of the state of knowledge: The diagnosis of MODY diabetes is more extensive than that of the most common types in the population - type 1 and type 2 diabetes.

Individual forms of MODY diabetes differ in the location of the mutation in the genome. As a result, the MODY group is heterogeneous, with individuals differing in the severity of symptoms, the treatment used and the presence of developmental abnormalities affecting various organ systems.

Sulfonylurea derivatives are a group of drugs that have been used to treat diabetes since the mid-20th century. Their mechanism of action is to stimulate insulin secretion, so it is necessary to preserve at least some of the function of the beta cells in the pancreatic islets when using them.

Summary: A collection of information on MODY diabetes is presented based on a review of research and scientific articles. In addition, the section on sulfonylureas provides an overview of first- and second-generation drugs and compares them. The article also highlights the important role of physical activity in managing diabetes and preventing complications.

Keywords: Diabetes; MODY; sulfonylurea derivatives; physical activity in diabetes;

Introduction

Diabetes is a group of metabolic disorders. By 2021, approximately 537 million adults (aged 20-79 years) suffer from diabetes - 1 in 10 adults in the world population [1]. More than 3 out of 4 people with diabetes live in low-income countries [1].

The number of people with diabetes is predicted to increase to 643 million by 2030 and 783 million by 2045 [1].

The disease is characterised by hyperglycaemia, which can be caused by inhibition of insulin secretion by the pancreas or the inability of cells to use insulin effectively [2].

Insulin is a hormone produced by the beta cells of the pancreatic islets that enables the transport of glucose into cells, the accumulation of glycogen in the liver and the regulation of blood glucose levels [2].

MODY - Maturity Onset Diabetes of the Young

This article describes MODY diabetes in more detail. The MODY form is the most common type of monogenetic diabetes [3]. The acronym MODY was first used by Fajans and Tattersall in 1975 to describe a group of patients with familial diabetes caused by an inherited autosomal dominant mutation in the gene responsible for insulin secretion [4]. It is currently estimated that this form of the disease accounts for 1-5% of all cases of diabetes [5].

The development of molecular diagnostics has allowed the identification of 14 subtypes of MODY diabetes [6]. The basic features in the diagnosis of this type of disease are early onset, autosomal dominant inheritance of a mutated gene [7].

However, in a study of MODY diabetes in 922 families, 11 out of 150 individuals had a de novo mutation responsible for the disease and no family history of an autosomal dominant gene variant or family history of hyperglycaemia [8].

The diagnosis of MODY diabetes is based on a high probability of disease, and diabetes is diagnosed based on standard tests, clinical assessment and genetic testing [7].

The criteria for a high probability of MODY are: persistent hyperglycaemia in young adults (up to 30 years of age); clinical disagreement with a diagnosis of type 1 or type 2 diabetes; diabetes in one or more first-degree relatives; absence of autoimmune damage to the pancreas and residual pancreatic beta cell function [9]. The incidence of MODY in Europe has been well studied. In the United Kingdom, this form of diabetes is estimated to account for 2.5% of the prevalence of diabetes, with similar figures in other countries - Poland, Norway, Germany, the Netherlands [10][11][6].

Diagnosis and differentiation

It is important to correctly diagnose diabetes in patients. Although this form of the disease is rare in patients with diabetes, it is particularly important to distinguish it from type 1 diabetes. Incorrect diagnosis leads to inappropriate treatment.

Anti-islet antibodies - anti-IA2 (anti-tyrosine phosphatase associated with pancreatic islet granules) and anti-GAD, which occur in autoimmune diabetes type 1 and LADA, are not present in patients with monogenic diabetes [12]. This was confirmed in a study of 508 patients. 227 patients with MODY 2 and 229 with MODY 3 and 98 people with type 1 diabetes diagnosed within 6 months. Among the participants, the following results were obtained: anti-GAD or anti-IA2 was present in 82% of people with type 1 diabetes, while <1% of patients with MODY had it. Conclusion of the study - the presence of anti-GAD and anti-IA2 antibodies is characteristic of type 1 and LADA and the occurrence of antibodies is very unlikely in patients with MODY, which allows the diagnosis to be excluded [13]. An important parameter in differentiating MODY from type 1 diabetes is the concentration of C-peptide, which is usually higher in MODY than in type 1 diabetes [12].

In differentiating MODY from type 2 diabetes, it is important to measure fasting insulin concentration and calculate the HOMA-IR index; a value greater than 2 indicates insulin resistance, which is characteristic of type 2 diabetes [12].

Diabetes mellitus type mody division

Maturity-onset diabetes of the youth is a form of the disease that can occur in various forms. From mild non-progressive hyperglycaemia, to forms that progress over time, to forms of the disease in which symptoms affect organ systems other than the pancreas.

MODY 1 - Caused by a mutation in the HNF-4A gene, which encodes the transcription protein - Hepatocyte Nuclear Factor [14]. In people with this form of the disease, there is a progressive increase in blood glucose concentration as a result of a weakened response of Langerhans cells to hyperglycaemia; the process of gluconeogenesis and glucagon production in the liver is also disturbed. As a result of impaired glycaemic control, patients develop microvascular complications of diabetes over time [15].

The HNF4A mutation also leads to impaired lipid synthesis, resulting in reduced serum triglyceride and lipoprotein levels [16].

MODY 2 - Caused by a mutation in the glucocinase gene - GCK. This disrupts the conversion of glucose to glucose-6-phosphate. It is a well-studied form of MODY, characterised by a mild, non-progressive course in which insulin secretion is stimulated at

higher glycaemic levels than in healthy people (HbA1c usually remains below 7.5%) [17]. Patients have no symptoms of diabetes and no tendency to ketoacidosis. In general, patients do not require pharmacotherapy, and appropriate diet and exercise are recommended [18].

MODY 3 - This is the most common form of MODY diabetes. It is caused by a mutation in the HNF-1A transcription factor gene. The disease is characterised by mildly elevated fasting glucose levels and very high glycaemia after glucose administration. Over time, insulin secretion decreases and glycaemic control deteriorates [14]. This form of the disease is extremely sensitive to the effects of sulfonylurea derivatives, as demonstrated in a randomised study by Pearson et al. - MODY 3 patients had an approximately 5-fold greater response to oral gliclazide than to metformin [19].

MODY 4 - a rare form of the disease caused by a mutation in the PDX-1 gene, which plays an important role in the development of the pancreas. In homozygous cases, there is a developmental defect - pancreatic agenesis [20]. Patients with this form of the disease develop type 2 diabetes at an early age [14].

MODY 5 - a rare form caused by the HNF-1B mutation. It often manifests as polycystic kidney disease and other genitourinary defects. Patients require early insulin therapy because the liver is resistant to insulin and therefore the effect of sulfonylurea derivatives is ineffective [15]. In a follow-up cohort study of 201 patients by Dubois-Laforgue et al., the results indicate that half of the patients start insulin therapy after diagnosis of the disease, and in 73% of cases it is necessary to switch from sulfonylurea derivatives to insulin due to poor glycaemic control [21].

MODY 6 - a very rare form caused by the NEUROD1/BETA2 mutation. The onset of the disease is variable, ranging from young adults to around 60 years of age [14]. Most cases require insulin treatment.

MODY 7 - a rare form caused by a heterozygous mutation in the KLF11 gene. Treatment requires insulin therapy [26].

MODY 8 - a rare form caused by a heterozygous mutation of the CEL gene. Treatment is with insulin [27].

MODY 9 - a very rare mutation of the PAX-4 gene. Insulin therapy is required [28].

MODY 10 - mutation of the INS insulin gene, resulting in the secretion of dysfunctional insulin. Mild course. Initially treated with diet, then over time with hypoglycaemic medication or insulin [29].

MODY 11 - Heterozygous mutations in the BLK gene. Treatment mostly with diet [30].

MODY 12 - Mutations in the ABCC8 gene, which encodes the ATP-gated potassium channel. Mutations in this gene are responsible for neonatal diabetes, but in some cases there may be increased insulin levels in newborns who develop diabetes later in life [22].

MODY 13 - KCNJ11 gene mutation. This mutation is responsible for persistent neonatal diabetes; patients can be effectively treated for a long time with sulfonylureas [23]. This form of MODY diabetes is caused by the p.Glu227Lys mutation in the KCNJ11 gene, which causes the disease to appear around the age of 20 in patients treated with sulfonylurea derivatives [24].

MODY 14 - a form of monogenic diabetes, APPLY-1 gene mutation; described in a study of 2 families [25].

Sulfonylurea derivatives

A group of oral hypoglycaemic medicines used in the treatment of diabetes.

The beginings of the use of this group of substances date back to the 40s of the 20th century, which makes them the longest-used drugs in the treatment of diabetes. The discovery of the effects of these substances occurred while searching for a cure for typhus.

Marcel Janbon observed that severe hypoglycaemia occured in experimental animals after administration of sulfamidothiodiazole [31].

Tolbutamide was the first sulfonylurea drug used in the pharmacotherapy of diabetes, introduced in 1956.

Sulfonylurea derivatives are drugs with a hypoglycaemic effect by increasing insulin secretion. They require preserved secretory activity of the beta cells of the pancreatic islets[9].

They act by binding to the SUR subunit of the ATP-dependent potassium channel (KATP), which is located in the plasma membrane of pancreatic beta-cells [32][33]. Substances from this group also have effects on other organs apart from the pancreas; because potassium channels are also found in other tissues.

The above-mentioned ion channels are composed of two types of subunits - the Kir 6.x subunit - which forms the channel lumen, and the SUR regulatory subunit, which is a receptor for the discussed group of drugs. Each ATP-dependent potassium channel consists of 4 units of both types [4]. After the drug molecule attaches to the SUR1 receptor, the potassium channel closes. As a result, the cell membrane of pancreatic beta cells becomes depolarized. As a result, calcium channels in the cell membrane open and calcium ions flow into the cell, which stimulates the secretory granules to secrete insulin.

Glucose has a similar effect on beta cell ion channels [33].

The next section will discuss some medicines from the sulfonylurea group.

Drugs of this group are used to treat diabetes in patients who have preserved beta cell function of the islets of Langerhans.

Tolbutamide - 1st generation derivative. The first drug used in the treatment of diabetes is a substance with a relatively weak and short antihyperglycemic effect (6-12 hours). It is well absorbed from the gastrointestinal tract and is transformed in the liver into inactive metabolites, excreted by the kidneys [33].

Glibenclamide - was introduced into treatment as the first of the second-generation preparations.

It presents a great hypoglycemic effect - while maintained the function of pancreatic beta cells, it strongly stimulates them to secrete insulin and works for a long time (18-24 hours). The potency is approximately 150x greater than that of Tolbutamide.

An additional peripheral effect of the drug is to increase the sensitivity of the liver to insulin.

In the process of drug metabolism, substances with antihyperglycemic effects are also produced. Glibenclamide is excreted both by the kidneys and the gastrointestinal tract; therefore, when renal function deteriorates, the risk of hypoglycemia increases [33].

Gliclazyde - a second generation sulfonylurea derivative. By acting on the beta cells of the islets of Langerhans, it stimulates them to secrete insulin. The drug is characterised by a quick onset but also a short duration of action. Gliclazyde metabolites present vascular effects - reducing sensitivity to epinephrine, inhibiting platelet aggregation and intensifying fibrinolysis; also restores the ability of blood vessels to dilate under the influence of NO, inhibiting atherogenic processes. The substances are mainly excreted in the urine. Gliclazide is a substance particularly insoluble in water. Thanks to the combination with a hydrophilic substance in the medicinal preparation, it was possible to increase the bioavailability and prolong the release of the drug for once-daily dosing [33].

Study confirmed the safety of the gliclazyde - Glucose control in type 2 diabetes with Diamicron MR (gliclazyde) versus GlimEpiride (GUIDE)

- Gliclazide MR, compared to Glimperide, was characterised by a 50% lower incidence of hypoglycemia, and was 4x safer for patients with impaired renal function [34].

Glipizide - a second generation derivative, is characterised by the fastest onset of action in its group, strongly stimulates insulin secretion - reaches maximum concentration 1 hour after administration, duration of action 16-24 hours and increases the sensitivity of peripheral

tissues to insulin. The drug is metabolised in liver and excreted mainly in the urine in the form of metabolites.

Glipizyde metabolism products are inactive, so there is no risk of hypoglycemia with reduced kidney function as a result of their accumulation in the body [33].

Glimperide - the newest drug in the group of second-generation derivatives. It acts on pancreatic cells, stimulating insulin secretion and in periphery it increases the sensitivity of the liver and muscles to its action.

The drug is metabolised in the liver to an active metabolite, which also has an antihyperglycemic effect, thanks to which, despite the short half-life of the original substance, the 24-hour effect is maintained. The drug can be used in patients with reduced renal function, because 58% of it is excreted by the kidneys, the rest from gastrointestinal tract [33].

Gliquidone - a second-generation drug with a very short duration of action (8 hours). Converted in the liver to inactive metabolites - no risk of hypoglycemia. 95% of it is excreted in the faeces [33].

Adverse effects of sulfonylurea derivatives - weight gain, hypoglycemia up to loss of consciousness, gastrointestinal disorders, temporary disturbances in the liver function, blood function impairment, allergic reactions, photosensitivity and bone marrow damage [35][36].

Physical activity in diabetes

Physical activity plays a very important role in maintaining health and proper body weight. One of the side effects of sulfonylurea drugs is weight gain; this is due to the stimulation of insulin release, which increases the transport of glucose to muscles and fat tissue [37]. Physical activity is recommended among patients with diabetes because it has many benefits. One of the most important is the increase in tissue sensitivity to insulin, which allows the use of lower doses of drugs in therapy and the reduction of body weight and loss of fat tissue, which has a beneficial effect on reducing the risk of diabetes complications related to the circulatory system [38][39]. It is recommended for patients with controlled diabetes to practice sports. The amount of physical activity recommended per week for children and adolescents is at least 60 minutes a day of medium-intensity exercise, preferably aerobic. Adults should perform 150-300 minutes of moderate-intensity physical activity or 75-150 minutes of vigorous-intensity exercise per week with a predominance of aerobic exercise[39][40].

Conclusions

Genetic testing is crucial for accurately distinguishing MODY from other forms of diabetes and for choosing the right treatment. Sulphonylureas, which are beneficial for certain subtypes of MODY, manage the condition by boosting insulin secretion. It is important to engage in physical activity to enhance overall well-being. Further investigation and acquisition of knowledge are required to enhance the identification, care, and outcomes for individuals with MODY-reducing complications and to improve the quality of life.

Disclosure

Author's contribution

Conceptualization: Rafał Makuch and Adam Kucharski; Methodology: Alicja Wawrzyniak; Software: Alicja Chrościcka; Check: Andrzej Czajka and Kamil Gała; Formal analysis: Konrad Pilarski and Martyna Dewicka; Investigation: Paweł Lenard and Sara Michalska; Resources: Kamil Gała; Data curation: Alicja Chrościcka; Writing - rough preparation: Adam Kucharski and Rafał Makuch; Writing - review and editing: Alicja Wawrzyniak and Konrad Pilarski; Visualization: Martyna Dewicka; Supervision: Sara Michalska; Project administration: Rafał Makuch and Paweł Lenard; Receiving funding - no specific funding.

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The authors deny any conflict of interest.

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