

PRECISION MEDICINE AND MONOGENIC DIABETES: ADVANCES, CHALLENGES, AND FUTURE PERSPECTIVES

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Abstract: Objective: Address recent advances in precision medicine in the diagnosis and treatment of monogenic diabetes, including MODY, neonatal diabetes and rare forms. **Method:** The report was prepared between April and May 2023, following the PVO strategy. A search was performed in the PubMed database, using descriptors such as “Monogenic Diabetes”, “MODY”, “Diabetes Maturity Onset of the Young”, “Neonatal Diabetes” and “Precision Medicine”. Sixteen articles selected after inclusion and exclusion criteria were analyzed, of the 88 found. **Results:** Precision medicine is revolutionizing the treatment of single-gene diabetes, identifying specific mutations and providing more effective therapies. Lifestyle and dietary modifications are recommended for HNF1A-MODY, and the use of sulfonylureas may be considered. In the case of NDM, it is possible to transition from insulin to sulfonylureas. In insulin-resistant diabetes, the use of insulin-sensitizing agents is preferred. Early diagnosis and insulin treatment are key for LADA. Precision medicine improves the quality of life for patients with monogenic diabetes. **Final considerations:** Precision medicine has brought significant advances in the diagnosis and treatment of monogenic diabetes, providing more effective therapies and better quality of life for affected patients. These advances represent an important step towards personalized medicine for single-gene diabetes. **Keywords:** Monogenic Diabetes; MODY, Neonatal Diabetes; Precision Medicine.

INTRODUCTION

Monogenic diabetes, a subgroup of diabetes caused by single-gene mutations that result in a defect in the function of beta cells, presents variations in its form of manifestation. Among these, MODY (maturity-onset diabetes of the young) stands

out, characteristic for manifesting before the age of 25 and being transmitted by autosomal dominant inheritance. With a relatively low incidence - only 50 cases per 100 million patients with diabetes - MODY is a peculiar form within the spectrum of monogenic diabetes (VALKOVICOVA T. et al., 2019). In addition, neonatal diabetes, also classified as monogenic, is a rare condition that manifests itself in infants, usually less than 6 months of age, with an estimated incidence of approximately 1 in every 100,000/200,000 births (CAMPBELL M.R., 2020).

Often, individuals with monogenic diabetes do not meet the criteria for an accurate diagnosis, and may be mistakenly classified as having type 1 (DM1) or type 2 (DM2) diabetes (ZHANG H. et al., 2021). Such incorrect diagnoses can result in inappropriate treatments and, consequently, long-term complications. Therefore, accurate diagnosis of the different forms of monogenic diabetes is essential to ensure effective and personalized treatment. Molecular genetic testing plays a crucial role in differentiating monogenic diabetes subtypes and distinguishing them from the more common forms of diabetes mellitus. Furthermore, the search for suitable biomarkers is a priority area of research that aims to assist in this process (CAMPBELL M.R., 2020).

The identification of monogenic diabetes genes has also allowed for revolutionary advances in precision medicine, many of them centered on inexpensive drugs such as sulfonylureas, widely used in type 2 diabetes. Sulfonylureas bind to and inhibit the regulatory subunit of one of the genes among those with higher incidence of mutations in the different forms of monogenic diabetes (BONNEFOND A.; SEMPLE R.K., 2022).

Faced with such a scenario, the objective of this study is to analyze recent developments in personalized medicine applied to the

identification and management of different types of monogenic diabetes, such as MODY, neonatal diabetes and other rare variations. This research is justified by the relevance of a more precise approach for the treatment and diagnosis of these individuals, taking into account their specific characteristics. Thus, it is possible to seek significant advances in clinical outcomes and quality of life of patients with monogenic diabetes.

METHODOLOGY

This article is a narrative review, carried out from April to May 2023 and developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. The guiding question was used for the elaboration of the research: "How can precision medicine be applied to the different types of monogenic diabetes, and what are the advances, challenges and future perspectives in the diagnosis and treatment of these disorders?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients with monogenic diabetes, including MODY, neonatal diabetes and other rare forms, who, through the use of precision medicine (variable), will be studied in order to discuss future prospects and clinical implications of advances in diagnosis and treatment through it (outcome). The searches were carried out through searches in the PubMed Central (PMC) database. The following descriptors were used in combination with the Boolean operators "AND" and "OR": "Monogenic Diabetes", "MODY", "Maturity onset diabetes of the young", "Neonatal Diabetes" and "Precision Medicine". From this search, the articles were subsequently submitted to the selection criteria. Inclusion criteria were: articles in French, English and Portuguese; published in the period from 2018 to 2022, which addressed

the themes proposed for this research, review, observational and experimental studies and made available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria.

After associating the descriptors used in the searched base (PubMed), a total of 88 articles were found. After applying the inclusion and exclusion criteria, 16 articles were selected, which were used to compose the collection.

RESULTS

MONOGENIC DIABETES

Monogenic diabetes is characterized as diabetes mellitus that results from a single mutation in a gene in a given individual. Prevalence ranges from 1 to 6% among known types. This can be classified as non-syndromic, which includes the most common forms, such as MODY and neonatal diabetes, and syndromic, which is rarer and covers some syndromes such as Wolfram Syndrome (ZHANG H. et al., 2021).

The form of diabetes with onset in young adulthood (MODY) is an autosomal dominant genetic disease and represents the majority of cases of monogenic diabetes (RAFIQUE I. et al., 2021). The classic clinical features of MODY include diagnosis at a young age, usually before age 25, and a positive family history, with some types presenting particularities (ZHANG H. et al., 2021). The genetic etiology of MODY was first discovered in 1990 and, to date, 14 genes have been identified (TOSUR MPHILIPSON L.H., 2022). According to some studies carried out in different populations, the most common types of MODY are MODY3 (21-64%) and MODY2 (8-63%), resulting from mutations in the HNF1A and GCK genes, respectively. In addition to these, other genes

are associated with MODY, such as HNF4A, HNF1B, INS, KCNJ11, ABCC8, PDX1, NEUROD1, KLF11, CEL, PAX4, BLK and APPL1 (SPERLING M.A. et al., 2018).

GCK (glucokinase) is an enzyme that catalyzes glucose phosphorylation and acts as a glucose sensor in pancreatic beta cells (RAFIQUE I. et al., 2021). Mutations in the GCK gene cause changes in the insulin secretion threshold. Therefore, patients with GCK-MODY usually have mild, persistent, non-progressive and asymptomatic fasting hyperglycemia, with HbA1c levels below 7.5% (ZHANG H. et al., 2021).

The HNF1A gene is expressed in organs such as the pancreas, liver and kidneys and is crucial for the development of pancreatic beta cells, insulin secretion and glucose cotransporter regulation (SGLT2), responsible for renal glucose reabsorption (VALKOVICOVA T et al., 2019). Mutations in this gene cause structural defects in the islets of Langerhans and an inefficient reabsorption of glucose in the renal tubules, leading to the emergence of HNF1A-MODY (TOSUR M., PHILIPSON L.H., 2022). MODY3 usually manifests itself between 6 to 25 years and ranges from mild symptoms, such as polyuria and polydipsia, to asymptomatic postprandial hyperglycemia. Initially, patients may have normal glucose levels in contrast to a glycosuria that precedes the progressive defect in insulin secretion by years. Additionally, the risk of microvascular and macrovascular complications depends on glycemic control (SPERLING M.A. et al., 2018).

Among the syndromic forms is neonatal diabetes, usually diagnosed up to 6 months of life. This type of diabetes is characterized by hyperglycemia present in the newborn and requires that the baby be treated with insulin up to 6 months of life. It can be classified as permanent or transient, when there is a resolution up to 18 months, but these cases

may have recurrence of the condition at some point in life (RAFIQUE I. et al., 2021). Most transient cases are related to overexpression of genes on chromosome 6q24 and the remainder are associated with mutations in the ABCC8 and KCNJ11 genes, also involved in the pathogenesis of the permanent type. Intrauterine growth retardation, polyuria and malnutrition are some of its manifestations, and in more severe cases neurological disorders and birth defects may occur (ZHANG H. et al., 2021).

PRECISION MEDICINE AND DIAGNOSIS OF SINGLE GENE DIABETES

The diagnosis of monogenic diseases has been the subject of increasing investigation, since for many years these diseases were diagnosed and treated as DM1 and DM2 (KOMAZEC J. et al., 2019). The first step towards an accurate diagnostic definition is clinical suspicion, which often proves to be a challenge (TOSUR M., PHILIPSON L.H., 2022); LYRA A. et al., 2022). According to Lyra A. et al. (2022), the Personalized Medicine for Diabetes Program at the University of Maryland conducted a study interviewing patients diagnosed with MODY, and the main complaint among them was the lack of knowledge of health professionals about this pathology. This highlights the crucial importance of establishing a screening method to facilitate the diagnosis and treatment of these diseases.

Decades of genetic mapping have led to the identification of three main etiologies: MODY, neonatal diabetes (NDM) and early childhood diabetes (VAXILLAIRE M.; FROGUEL P., 2016). Heterozygous variants in the genes GCK (glucokinase) (MODY 2), HNF1A (hepatocyte nuclear factor 1 alpha) (MODY 3) and HNF4A (hepatocyte nuclear factor 4 alpha) (MODY 1) are the most frequent,

representing together more than 95% of the known genetic causes of MODY.

NDM is a highly heterogeneous disease with more than 25 known genetic alterations, presenting with both dominant and recessive inheritance patterns. It is diagnosed in the first six months of life, due to its high severity of cellular dysfunction. About 70% of NDM cases are methylation abnormalities in the 6q24 region, causing transient diabetes. Other genes involved are KCNJ11/Kir6.2 and ABCC8/SUR1, responsible for encoding constituents of the ATP-dependent potassium channel, in addition to the INS and ZFP57 genes, which cause persistent hyperactivity of this channel (VAXILLAIRE M.; FROGUEL P., 2016 ; TOSUR M., PHILIPSON L.H., 2022).

There is still no consensus on which molecular technique is more reliable for diagnosing monogenic diseases. However, the RainDance PCR enrichment technology and the SureSelect exon capture method have shown high sensitivity and low cost as a screening method, directing which patients must be screened for more complete genetic mapping, such as Dideoxy sequencing (Sanger), which is defined as the gold standard (HARRIS A. et al., 2018).

After diagnostic confirmation of MODY, it is important to perform genetic tests on the patient's family members in order to determine the likelihood of developing diabetes in the future (SPERLING M.A. et al., 2018). The patient's family history is fundamental for requesting genetic analysis for monogenic diabetes. Indicators such as diabetes diagnosed in at least one family member before age 25, the presence of at least two first-degree relatives with diabetes, or an autosomal dominant inheritance pattern spanning at least three generations must raise the possibility of monogenic diabetes., 2021). Today, the diversity of monogenic diabetes is more than just observed and known; it is

also determined as an important factor in the onset and monitoring of the risk of the disease (SOUSA M. et al., 2022).

Regarding the divergence between the use of screening methods, it is relevant to discuss that Sperling M.A. et al. (2018) argue that screening is cost-effective due to the reduction in treatment costs and complications. However, Vaxillaire M. and Froguel P. (2016) argue that the prevalence only slightly increased with the implementation of genetic screening, making it less cost-effective. This divergence still needs to be further investigated and discussed in the scientific community.

PRECISION MEDICINE AND THE TREATMENT OF SINGLE GENE DIABETES

Most patients with MODY can be treated with oral sulfonylureas, which optimally control hyperglycemia by bypassing the molecular defect and activating the potassium channel. It is fundamental that the patient has adequate control of the diet, which, in mild cases, can resolve the problem without drug therapy. Therefore, performing genetic tests to determine the mutation of each type of MODY is of great importance (MARUCCI A. et al., 2022).

Patients with the HNF1A-MODY mutation can be treated without medication if the HbA1c is < 6.5%. Those who fit this criterion can be treated with improvements in lifestyle and a saccharide-free diet. If good resolution is not observed, sulphonyureas can be considered as the first choice of treatment. The recommended dose is a quarter of the starting dose in adults, which must be progressively increased in order to improve glycemic control. If glycemic control is not established, insulin can be used (DELVECCHIO M. et al., 2020).

The HNF4A gene, of monogenic diabetes, may be inherited from a paternal mutation in

fetuses of pregnant women. Children who have this gene can be born with high birth weight, which is compared to the sibling who does not carry the gene, those who have 790g more than the sibling without the gene, and can develop macrosomia. Treatment must be cautious, one option is glibenclamide, a sulfonylurea that crosses the placental barrier, but its use may contribute to the risk of increased birth weight and, in addition, may cause neonatal hypoglycemia. So far, there is no evidence of teratogenicity with the use of glibenclamide. As another option, sulfonylurea therapy can be replaced by insulin in the pre-pregnancy phase. Therefore, fetal growth must be monitored after 28 weeks, every 15 days by ultrasound, and in some cases, intervene with early birth between 35 and 38 weeks (DELVECCHIO M. et al., 2020).

Regarding the improvement of metabolic control and consequently the quality of life in neonatal diabetes mellitus (NDM), which is a monogenic form of diabetes that occurs predominantly in the first 6 months of life. It is estimated that around 30% of transient cases of NDM (TNDM) will result in a stimulatory mutation in the KATP channel genes ABCC8 and KCNJ11. Thus, most patients who suffer from this KCNJ11 mutation, who are on insulin therapy, will be able to use sulfonylurea to improve these purposes. The change in therapy takes place in a hospital environment, aiming to improve patient safety, thus, it is recommended to measure glucose before, two hours after each meal and at bedtime. (LYRA A. et al., 2022)

According to Greeley S.A.W. et al. (2018), almost half of the types of neonatal diabetes correspond to “de novo” or inherited mutations in potassium subunits. In this context, the drug of choice is sulfonylureas, which block ATP-sensitive potassium channels, promoting less hypoglycemia compared to insulin. Thus, it is concluded that this is a low-cost and

effective treatment for this type of monogenic diabetes (GREELEY S.A.W. et al., 2018).

There are different mutations in genes as causes of MODY subtypes, among them the most common are GCK, HNF1A, HNF4A and HNF1B. In the first mutation in which moderate fasting hyperglycemia occurs from birth, it does not require any treatment, unless you are pregnant, and the treatment of choice is insulin. In HNF1A, in which glycemia increases with age, a dose of sulfonylureas is used in low doses, including in pregnancy in the first two trimesters, the treatment is repeated for the HNF4A gene. HNF1B, on the other hand, requires systemic screening for renal cysts, exocrine pancreatic function, and genital abnormalities. Therefore, it is important to recognize the mutation of each gene, through genetic tests, in order to have an effective and optimized treatment (MARUCCI A. et al., 2022).

With regard to the treatment of severely insulin resistant diabetes, it is seen that most plasma insulin concentrations are extremely high. Thus, it is of paramount importance to choose a line of treatment that benefits the therapy of insulin-sensitizing agents compared to secretory agents, such as sulfonylureas. (BONNEFOND A.; SEMPLE R.K., 2022)

In MODY diabetes, patients have impaired glucose-induced insulin secretion at around 1% to 4% per year. The HNF1A-MODY form, the most common variant ever reported, causes a greater likelihood of hypoglycemia with

sulfonylurea than other MODYs. Therefore, diet and exercise control is necessary, however, follow-up by an endocrinologist is of great importance, as hypoglycemia can be a risk (BONNEFOND A.; SEMPLE R.K., 2022).

Also, latent autoimmune diabetes in adults (LADA) can be confused with type 2 diabetes or MODY, as the symptoms can be similar. The correct diagnosis is essential to direct the appropriate treatment. For example, while patients with MODY can usually be treated with oral therapy, patients with LADA usually need insulin therapy (ANDERSEN M.K. et al., 2022).

FINAL CONSIDERATIONS

Monogenic diabetes is a subgroup of diabetes mellitus that arises from mutation in a single gene. Among the most well-known forms are MODY (Maturity Onset Diabetes of the Young) and neonatal diabetes. These diseases are often misdiagnosed and treated as type 1 (DM1) or type 2 (DM2) diabetes, which can lead to further complications. In view of this, it is clear that precision medicine is capable of identifying the specific mutation of each gene, thus enabling early diagnosis and adequate targeting of treatment. With this study, it is observed that such advances represent a more effective and personalized therapy, consequently providing a better quality of life for patients with monogenic diabetes.

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