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Review

Monogenic Diabetes: Genotype, Clinical Phenotype, and Treatment: A Narrative Review

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Abstract

Monogenic Diabetes (MD) refers to a rare and newly identified type of diabetes caused by a defect in a single gene. This condition is marked by persistent hyperglycemia resulting from genetic defects passed down through families in various inheritance patterns, including Mendelian inheritance (dominant, recessive), or non-Mendelian inheritance (mitochondrial inheritance). Additionally, MD can also arise from new mutations that occur for the first time in an individual and are not inherited from either parent, known as de novo mutations. Monogenic forms of diabetes contribute to approximately 5% of pediatric diabetes cases. The etiology of MD involves two main mechanisms: one, multiple gene mutations that disrupt the formation or function of pancreatic β-cells, and two, defects in the insulin receptor that impair insulin action. These genetic abnormalities are primarily responsible for the clinical manifestation of diabetes in affected individuals. Despite its significance, there is a widespread lack of awareness about MD, leading to frequent misdiagnosis such as either type 1 or type 2 diabetes. This issue is exacerbated in regions with high rates of consanguinity, where monogenic diseases are more prevalent and require heightened clinical vigilance. Molecular genetic testing is the cornerstone of diagnosing MD, providing essential information for an accurate diagnosis, and enabling proper genetic counseling for affected families. This diagnostic approach is crucial for distinguishing MD from other types of diabetes, ensuring appropriate management and treatment tailored to the specific genetic mutation involved. This review incorporates a comprehensive literature analysis, based on data gathered from PubMed and Google Scholar. We will discuss the classification of MD, its genotypes and phenotypes, as well as treatment approaches for its various types. By highlighting these aspects, we hope to improve the recognition, diagnosis, and management of this rare form of diabetes.

Keywords: *Monogenic Diabetes mellitus, maturity-onset diabetes of the young, neonatal diabetes, Diabetes, Monogenic disease, Genetic mutation*

Introduction

Diabetes is a chronic metabolic disorder characterized by persistently high blood glucose levels. This condition arises either from the pancreas's beta cells failing to produce sufficient insulin or from the body's cells becoming resistant to the insulin that is produced. Insulin is a hormone crucial for regulating blood sugar levels, and its deficiency or resistance leads to the hallmark hyperglycemia of diabetes. There are several types of diabetes mellitus (DM), with type 1 diabetes being the most common type among children, type 2 diabetes more predominant in adults, and gestational diabetes occurring mainly in adults during pregnancy (1–3). Type 1 diabetes is typically an autoimmune condition where the immune system attacks and destroys beta cells, leading to little or no insulin production. Type 2 diabetes is primarily associated with insulin resistance, often exacerbated by factors such as obesity, physical inactivity, and genetic predisposition. Gestational diabetes occurs during pregnancy and is usually resolved after childbirth, although it increases the risk of developing type 2 diabetes later in life (3). In addition to these common forms, other rare types of diabetes present unique clinical features and pathologies. These include diabetes resulting from monogenic defects in β-cell function, where mutations in a single gene impair insulin production or secretion, or gene mutations affect insulin action. Monogenic diabetes (MD) is a hereditary form caused by specific genetic mutations and accounts for up to 5% of pediatric diabetes cases. This form of diabetes is notable for its early onset and often familial pattern, requiring tailored diagnostic and therapeutic approaches (4,5).

Historically, all patients presenting with diabetes were broadly classified into either type 1 DM or type 2 diabetes, based on the age of onset and the requirement for insulin therapy. Type 1 diabetes, often diagnosed in childhood or adolescence, is characterized by an absolute need for insulin due to the destruction of insulin-producing beta cells. In contrast, type 2 diabetes typically had a later onset and was initially managed without insulin, being associated more with insulin resistance. It was not until 1975 that Tattersall RB and Fajans SS identified a distinct subset of patients who exhibited a familial form of diabetes (6). This group of patients presented with diabetes during adolescence or early adulthood, but shared characteristics more commonly associated with type 2 diabetes, such as a milder disease course and an initial lack of insulin dependency. This form of diabetes demonstrated an autosomal dominant pattern of inheritance, suggesting a specific genetic defect. Their research led to the recognition of what is now known as Maturity Onset Diabetes of the Young (MODY), a form of MD resulting from mutations in a single gene affecting beta-cell function. Unlike the more common polygenic types of diabetes, MODY has a clear genetic basis, often presented in multiple generations within a family. This discovery has significant implications for diagnosis and treatment, as patients with MODY may benefit from different therapeutic approaches compared to those with type 1 or type 2 diabetes (6).

In recent decades, revolutionary advancements in molecular genetic testing have led to the detailed characterization of MD. This form of diabetes arises from a defect in a single gene, which can be inherited in various patterns: autosomal dominant, autosomal recessive, or non-Mendelian. In some cases, the genetic defect may occur as a new, de novo mutation with no prior family history. To date, researchers have identified over 50 different genetic subtypes of MD, each associated with specific gene mutations (5).

The availability of genetic testing has expanded globally, enabling more precise diagnosis and management of MD. Traditional genetic diagnostic methods primarily utilize Sanger sequencing, which remains the gold standard for detecting specific genetic mutations (7). This method provides high accuracy and reliability in identifying single nucleotide changes and small insertions or deletions within genes. However, Sanger sequencing is typically complemented by additional assays, such as multiplex ligation-dependent probe amplification, to detect larger genetic alterations like partial or whole gene deletions or duplications. This kind of genetic testing for MD is often targeted

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based on the patient's clinical phenotype. This means that the choice of genes to be tested is informed by specific characteristics observed in the patient, such as age of onset, family history, and particular clinical features (5, 7). Recently, the advent of next-generation sequencing (NGS) has revolutionized genetic testing by enabling the simultaneous analysis of multiple genes in a single, cost-effective procedure. This advanced technology is increasingly replacing classical genetic testing methods in many institutions, offering greater efficiency and broader diagnostic capabilities (8). Selecting diabetic patients for genetic testing should be based on a comprehensive evaluation of their clinical, immunological, and biochemical phenotypes. Due to the low prevalence of MD, widespread lack of awareness, and the necessity for advanced diagnostic methods, many cases are often misclassified as type 1 or type 2 diabetes. Even in developed healthcare systems, at least 80% of all monogenic instances of diabetes go undetected (5). However, identifying patients with MD is crucial for several reasons. It enhances clinical care by allowing for more accurate predictions of disease prognosis and informing the most appropriate management strategies, including tailored pharmacological treatments. Additionally, a proper diagnosis has significant implications for family genetic counseling. It enables extended genetic screening of other diabetic family members, which may lead to reclassification and better management of their diabetes (7). It is important to note that the prevalence of MD is higher in populations with a high rate of consanguinity. In regions where consanguinity rates exceed 50%, like Saudi Arabia, the incidence of MD is expected to be significantly higher compared to areas where the rate is less than 30%, such as in many European countries (9). In this review, the aim is to enhance awareness and encourage health practitioners to maintain a high index of suspicion for MD by providing a summary of the typical causes of MD, outline clinical features, and shares experiences with different screening, diagnosis, and management strategies.

Review

The study includes a thorough literature analysis that covers research done over the last 20 years and is based on data taken from the PubMed and Google Scholar databases. Apply keywords like "pathophysiology," "genetics," "phenotypes," "Monogenic Diabetes," "MODY," and "treatment," as well as the Boolean operators AND, OR, and NOT, aid in refining searches. A structured search strategy used to identify relevant studies, followed by title, abstract, and full-text screening. The focus will be on the classification, pathophysiology, and phenotypes of MD, as well as the treatment approaches for its various types. By shedding light on these aspects, we hope to improve diagnosis and management, ultimately leading to better patient outcomes.

Medical suspicion of MD is particularly increased in cases with certain clinical features. These include a strong family history of diabetes, early onset of diabetes (typically before the age of 35), diabetes that appear in the neonatal period, and the presence of atypical characteristics not commonly associated with type 1 or type 2 diabetes (7). For example, children or adolescents presenting with mild hyperglycemia without ketosis, non-insulin dependency. Additional unusual clinical characteristics, such as non-obesity, the absence of islet autoantibodies, and detectable C-peptide levels, may warrant further investigation into genetic testing. (7). To aid in identifying candidates for testing, diabetic experts have developed the MODY probability calculator, an algorithmic tool designed to estimate the likelihood of MD in patients with diabetes onset before 35 years of age. This calculator considers various factors, such as age of onset, family history, and specific clinical and biochemical markers, to provide a risk assessment for MD; particularly the MODY subtype (7, 8). The classification MD aligns with the professional consensus in pediatric diabetes and includes four distinct clinical presentations (7):

A. Neonatal Diabetes Mellitus (NDM): Diabetes that are presented before 6 months of age.

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B. MODY: Autosomal dominant familial mild hyperglycemia or diabetes.

C. Genetic Syndromes Associated with Diabetes: Diabetes is associated with extra-pancreatic features, such as those found in mitochondrial MD mellitus.

D. Monogenic Insulin Resistance Syndromes: Diabetes resulting from defects in the insulin receptor, leading to severe insulin resistance.

Clinical presentation of MD

Atypical characteristics of type 1 or type 2 diabetes that may indicate MD in children include the onset of diabetes before six months of age, an absence of autoimmune markers, and the presence of other associated features such as congenital anomalies. Additionally, a family history of diabetes, particularly in the affected parent, can be a significant indicator. In these cases, β-cell function is usually preserved, resulting in low insulin requirements and measurable levels of C-peptides. Furthermore, typical features of type 2 diabetes, such as obesity, acanthosis nigricans (darkened patches of skin, often in body folds), and other signs of metabolic syndrome, are usually absent in children with MD (7).

MD classifications:

NDM:

Over 30 genetic subtypes of neonatal diabetes have been identified. The most common genetic causes of diabetes that appear in the neonatal period and early infancy are listed in (**Table 1**).

Table 1: The most common phenotypes and genotypes of Neonatal Diabetes

MD phenotype	Gene / Mode of inheritance	Frequency of cases	Clinical Phenotype	Phenotype MIM number	Treatment	Reference
Chromosome 6q24 PLAGL1/HYMAI	Maternally imprinted locus at 6q24	Between 1 in 215,000 and 1 in 400,000 babies	Severe intrauterine growth restriction, macroglossia, umbilical hernia, transient neonatal diabetes	601410	Insulin therapy	(12–14)
Mutations in the KATP channel	KCNJ11 or ABCC8/ AD, AR	Commonest cause of neonatal diabetes in Europe	Transient or permanent neonatal diabetes, Intrauterine growth restriction, developmental delay (DEND)	618856 618857	Sulfonylurea drugs	(17–21)
Mutations of the Insulin Gene	INS/AD, AR	The third cause of neonatal diabetes	Permanent neonatal diabetes	618858	Insulin therapy	(7)

Type 1 diabetes is extremely rare in the first year of life, particularly before the age of 6 months. Consequently, all patients diagnosed with diabetes under 6 months of age should undergo genetic testing for NDM. Over 80% of children who develop diabetes before 6 months can be accurately diagnosed through genetic testing, enabling specific treatments tailored to certain genetic defects (7). Although genetic causes are less common in infants diagnosed between 6 and 12 months, genetic testing is still recommended for those with negative autoantibody markers, extra-pancreatic associations, congenital anomalies, or a positive family history of diabetes (10). Infants with NDM often present with a small gestational age at birth due to in-utero insulin deficiency (11). There are

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more than 20 known genetic causes for NDM. Based on the clinical phenotype, NDM can be classified into two categories: permanent neonatal diabetes mellitus (PNDM), which requires lifelong treatment to manage hyperglycemia, and transient neonatal diabetes mellitus (TNDM), which typically resolves within a few weeks or months but may relapse later in life (7).

The most common gene defects in NDM are:

TNDM, which results from imprinting anomalies on chromosome 6q24, approximately two-thirds of neonatal diabetes cases are caused by defects in a maternally imprinted region on chromosome 6q24, which invariably leads to TNDM (12). Neonates with diabetes due to 6q24 abnormalities frequently present with severe intrauterine growth retardation from birth. Additionally, about one-third of these infants exhibit macroglossia (an abnormally large tongue) and umbilical hernias. These neonates typically develop severe but non-ketotic hyperglycemia very early, usually within the first week of life (13). In most cases, treatment involves insulin therapy. Insulin doses can be gradually reduced, and by 12 to 14 weeks of age, most infants no longer require treatment due to the high rate of remission. However, in a large cohort study of children followed until 18 years of age, diabetes recurred in at least 50–60% of these individuals. Therefore, it is crucial for parents of children with TNDM to be counseled about the high risk of diabetes relapse. Annual HbA1c testing may be beneficial for monitoring (14, 15). (**Table 1**)

PNDM**,** which requires lifelong treatment: The most commonly known cause of NDM in outbred populations is mutations in the ATP-sensitive potassium (KATP) channel genes or the INS gene, which can lead to PNDM (16).

Mutations in the KATP channel genes, (Table 1), activating mutations in either of the genes encoding the two subunits of the KATP channel of the β-cell membrane, KCNJ11 or ABCC8, are responsible for most cases of permanent neonatal diabetes. These mutations result in the most prevalent type of PNDM (16). This form of diabetes is successfully treated with sulfonylureas, a class of oral medications that stimulate insulin secretion. Additionally, mutations in the KATP channel genes are the second most common cause of TNDM (17).

Normally, the closure of the KATP channel depolarizes the cell membrane, leading to the influx of calcium through voltage-gated calcium channels. This calcium influx triggers the exocytosis of insulin granules, releasing insulin. The gene KCNJ11 encodes the inner subunit (Kir6.2) of the KATP channel, while ABCC8 encodes the outer subunit (SUR1). Mutations in these genes cause the KATP channels to remain inappropriately open, preventing the secretion of insulin from beta cells (18). Clinical presentation typically includes the onset of diabetes before 6 months of age, although diagnosis after 6 months is also possible. A lot of the time, diabetic ketoacidosis is present at diagnosis, and patients often have a small-for-gestational-age birth weight due to intrauterine growth restriction (19). Children with KCNJ11 mutations, especially those with permanent forms of neonatal diabetes, may exhibit an increased frequency of attention deficit hyperactivity disorder, developmental delays, and seizures, a condition known as DEND syndrome (Developmental delay, Epilepsy, and Neonatal Diabetes), due to the mutation of KATP channels in the brain (20). Treatment involves high doses of sulfonylureas, typically 0.5–1 mg/kg/day of glyburide or higher, depending on the specific mutation. Sulfonylurea therapy not only improves glycemic control but may also enhance neurological function, with earlier initiation providing greater benefits (21).

In cases where the parents are consanguineous, the most common causes of PNDM include Wolcott-Rallison syndrome and homozygous mutations in the glucokinase (GCK) gene. Wolcott-Rallison syndrome is characterized by early-onset diabetes, skeletal dysplasia, and liver dysfunction, among other systemic complications. Homozygous mutations in the GCK gene, which encodes the enzyme glucokinase critical for glucose sensing in pancreatic beta cells, lead to severe insulin deficiency from birth due to impaired glucose metabolism (22).

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Mutations of the Insulin Gene **(Table 1),** both dominant and recessive mutations in the INS gene are recognized as common causes of NDM. These mutations result in insufficient production or improper folding of insulin, leading to diabetes. Infants with these mutations typically present with low birth weight due to intrauterine insulin deficiency, followed by persistent postnatal hyperglycemia. The clinical phenotype often includes significant challenges in maintaining normal glucose levels from birth. The management of affected infants involves insulin replacement therapy to control blood glucose levels and mitigate the symptoms of diabetes (7, 23).

B. Autosomal dominant familial mild hyperglycemia or diabetes. (MODY) Diabetes:

MODY diabetes typically presents at a young age due to beta-cell dysfunction, leading to impaired insulin secretion. The abbreviation MODY, reflects the early onset and the maturity-onset-like phenotype of this form of diabetes (6). Refer to (**Table 2**) for more details on the genetic subtypes and characteristics of MODY.

Clinical Presentation of MODY Diabetes **(Table 2):** The clinical presentation of MODY diabetes varies significantly depending on the specific gene mutation involved. Diagnosing MODY can be challenging, as it may be mistaken for either type 1 or type 2 DM. This form of diabetes typically presents before the age of 25 and is often associated with a positive family history. Patients with MODY generally do not develop ketotic hyperglycemia or pancreatic autoantibodies. Approximately 6.5% of children with antibody-negative diabetes are diagnosed with a form of MODY (24). There are various genetic subtypes of MODY, each with distinct responses to therapy, complication rates, ages of onset, and associated extra-pancreatic defects affecting organs such as the kidneys, liver, and intestines (25). MODY genetic defects primarily cause beta-cell dysfunction, impairing insulin release by affecting insulin sensing, glucose uptake in beta cells, or the activation of ATP-dependent potassium channels. Understanding the specific genetic mutation is crucial for diagnosis, tailoring treatment, and managing complications effectively (26).

Today, more than 14 different MODY mutations have been identified. The most common genes involved in MODY include GCK, HNF1A, HNF4A, HNF1B, INS, NEUROD1, PDX1, PAX4, ABCC8, KCNJ11, KLF11, CEL, BLK, and APPL1. Below are descriptions of the most common gene variants associated with MODY **(Table 2)**.

HNF1A (MODY 3): Mutations in the hepatocyte nuclear factor 1 alpha gene lead to MODY 3, which is characterized by progressive beta-cell dysfunction and sensitivity to sulfonylureas.

HNF4A (MODY 1): Mutations in the hepatocyte nuclear factor 4 alpha gene cause MODY 1, often presenting with a marked sensitivity to sulfonylureas and a higher risk of neonatal hyper-insulinemic hypoglycemia.

GCK (MODY 2): Mutations in the glucokinase gene result in MODY 2, characterized by mild, stable fasting hyperglycemia that usually does not require pharmacological treatment.

HNF1B (MODY 5): Mutations in the hepatocyte nuclear factor 1 beta gene lead to MODY 5, which is associated with renal cysts and other urogenital abnormalities, along with diabetes.

PDX1 (MODY 4): Mutations in the pancreatic and duodenal homeobox 1 gene result in MODY 4, which involves beta-cell dysfunction and pancreatic agenesis in some cases.

For further details on the genetic variants and their specific characteristics, refer to **(Table 2)**.

HNF1A-MODY (MODY 3), Hepatocyte nuclear factor 1-alpha (HNF1A) mutations, responsible for MODY 3, disrupt normal glucose transport and metabolism in the mitochondria of pancreatic beta cells. This genetic defect leads to ongoing beta-cell dysfunction and a reduced renal threshold for glucose, causing glycosuria at lower blood glucose levels. HNF1A-MODY accounts for approximately 60% of all MODY cases. The onset of HNF1A-MODY typically occurs between the ages of 21 and 25. The gene defect has a penetrance rate of about

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60%, meaning that 60% of carriers will develop diabetes by the age of 25, and around 80% by the age of 35 (27).

Initially, patients are usually managed with dietary adjustments. However, as the disease progresses, patients may experience post-meal hyperglycemia and beta-cell failure, necessitating treatment with sulfonylureas. Sulfonylureas are effective in enhancing insulin secretion and can delay the need for insulin therapy for several years (28). A randomized controlled trial demonstrated the effectiveness of a glucagon-like peptide 1 (GLP-1) agonist in treating MODY 3 patients, offering another therapeutic option (29). Patients with HNF1A-MODY have a comparable risk of developing diabetic complications, such as retinopathy, nephropathy, and cardiovascular disease, similar to those with type 1 and type 2 DM. Early diagnosis and appropriate management are crucial in mitigating these risks (30).

Table 2: The most common phenotypes and genotypes of MODY Diabetes

MD phenotype	Gene / Mode of inheritance	Frequency of cases	Clinical Phenotype	Phenotype MIM number	Treatment	Reference
***HNF1A* (MODY 3)**	HNF1A/AD	The most common type of MODY, 50 to 70 % of MODY cases	Progressive diabetes, early age of onset, diabetic complications	600496	Diet, Sulfonylureas, Insulin therapy, Glp1 agonist	(27–30)
HNF4A (MODY1)	HNF4A/AD	10 % of MODY cases	Progressive diabetes, Neonatal macrosomia and hyper-insulinemic hypoglycemia, chronic diabetic complications	125850	Diet, Sulfonylureas, Insulin therapy. Glp1 agonist	(7, 31)
***GCK* (MODY 2)**	GCK/AD	30 % of MODY cases	Mild non-progressive diabetes, Diabetes-related complications are extremely rare.	125851	No treatment Except for affected pregnant to prevent macrosomia	(32, 33)
HNF-1β (MODY5)	HNF-1β/AD	5 % of MODY cases	Progressive diabetes, progressive renal failure, renal cysts, hyperuricemia	125853	Insulin therapy	(34, 35)
PDX1 (MODY 4)	IPF/PDXI/AD	rare	Pancreatic agenesis, PNDM in homozygote	606392	Diet, Insulin therapy or oral hypoglycemic agents	(7, 36)

HNF4A-MODY (MODY 1), Hepatocyte nuclear factor 4 alpha (HNF4A) mutations, which account for around 3%-5% of all MODY cases, are responsible for MODY 1 (30). This form of diabetes results from loss-of-function mutations in the HNF-4α gene located on chromosome 20q13. HNF-4α is highly expressed in the liver, kidneys, and pancreatic β-cells, where it regulates the expression of genes involved in glucose transport, metabolism, nutrient-induced insulin secretion, triglyceride metabolism, and lipoprotein biosynthesis (31). Patients with HNF4A mutations exhibit a gradual decline in insulin secretion beginning in infancy, similar to MODY 3. These mutations are characterized by macrosomia and hyper-insulinemic hypoglycemia during the neonatal period, which typically improve during infancy. However, as the child grows, insulin production declines, and hyperglycemia, along with the full clinical picture of diabetes, usually manifests during

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adolescence. If left untreated, chronic hyperglycemia can damage small blood vessels in the eyes and kidneys, leading to diabetic retinopathy and nephropathy, respectively (7).

Treatment for hyperglycemia in patients with HNF4A mutations is effectively managed with low-dose sulfonylureas, like the treatment for MODY 3. These medications enhance insulin secretion and are often the first line of treatment, remaining effective for many years (7).

In addition to diabetes, some HNF4A mutations can present with atypical Fanconi syndrome, characterized by nephrocalcinosis and renal impairment. Therefore, patients with HNF4A-MODY may require monitoring and management for both diabetes and potential kidney-related complications (7).

GCK-MODY (MODY 2)**,** Glucokinase MODY (GCK-MODY), also known as MODY 2, is a common subtype of MD frequently observed in pediatric diabetes clinics. This form of diabetes accounts for 32 % of all MODY cases and presents a consistent clinical picture among affected individuals (30). Patients with GCK-MODY exhibit non-progressive mild hyperglycemia from birth. Hemoglobin A1c levels are mildly elevated, typically below 7.5%, and these patients generally do not experience postprandial hyperglycemia (32).

Most cases of GCK-MODY are identified incidentally when blood glucose levels are measured for unrelated reasons. Blood glucose levels in these patients do not rise significantly over time, making chronic complications of diabetes uncommon. As a result, individuals with GCK-MODY rarely require any treatment, except during pregnancy. In such cases, an affected mother with GCK-MODY may need management to prevent fetal overgrowth in an unaffected fetus due to her mild hyperglycemia (33).

Hepatocyte Nuclear Transcription Factor 1beta (MODY 5), HNF1B-MODY (MODY 5) caused by mutations in HNF1B gene located on chromosome 17q12. This transcription factor regulates genes involved in various embryonic developmental processes, including those of pancreatic beta cells. The diabetes syndrome in MODY 5 typically presents during adolescence and is frequently associated with renal abnormalities, such as renal cysts, renal dysplasia, and urinary tract malformations. Additionally, individuals often have a low birth weight (34).

Renal dysfunction is a significant concern for patients with MODY 5, with half developing end-stage renal disease by the age of 45, independent of diabetic kidney disease. These patients often become dependent on insulin therapy earlier due to hepatic insulin resistance and pancreatic hypoplasia (7, 34). Other clinical features of HNF1B-MODY may include hyperuricemia, gout, low HDL cholesterol levels, and elevated triglyceride levels. The presence of these metabolic abnormalities, along with the characteristic renal issues and early-onset diabetes, are key indicators for diagnosing MODY 5 (35).

Pancreatic and Duodenal Homeobox 1 Maturity-Onset Diabetes of the Young (MODY 4): PDX1-MODY (MODY 4) caused by mutations in the pancreatic and duodenal homeobox 1 (PDX1) gene, a crucial transcription factor containing a homeodomain. This gene plays a significant role in regulating insulin gene expression and the development of the pancreas. Heterozygous mutations in the PDX1 gene lead to defective insulin secretion, resulting in diabetes. In contrast, homozygous mutations cause more severe outcomes, including PNDM and exocrine pancreatic insufficiency. Children with MODY 4 are present with early-onset diabetes due to impaired insulin secretion from dysfunctional beta cells. Treatment options for managing MODY 4 include dietary interventions to control blood glucose levels, oral anti-diabetic medications to stimulate insulin secretion or enhance insulin sensitivity, and insulin therapy for cases where endogenous insulin production is insufficient (36).

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Diabetes is associated with extra-pancreatic features. (Genetic syndromes associated with diabetes):

Diabetes can be linked with extra-pancreatic features, particularly in the context of genetic syndromes. A monogenic disorder should be suspected in any child presenting with diabetes accompanied by multi-system extra-pancreatic features, as it may be associated with other genetic syndromes (7). The most common genetic syndromes related to diabetes are detailed in **(Table 3)**, which will be discussed below; include conditions such as Wolcott – Rallison syndrome, IPEX FOXP3 syndrome, Mitochondrial diabetes, Wolfram syndrome, Rogers syndrome.

Table 3: The most common phenotypes and genotypes of diabetes-associated syndromes

MD phenotype	Gene / Mode of inheritance	Frequency of cases	Clinical Phenotype	Phenotype MIM number	Treatment	Reference
Wolcott – Rallison syndrome	EIF2AK3/ AR	Most common cause of PNDM in consanguineous pedigrees	Early-onset DM, epiphyseal dysplasia, and hepatic and renal dysfunction.	226980	Insulin therapy	(37, 38, 51)
IPEX Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome	FOXP3/ X-linked recessive	1 in 1.6 million people.	Early onset type 1 DM, severe enteropathy, eczema, anaemia, thrombocytopenia, and hypothyroidism	304790	Insulin and thyroid hormones supplementation hematopoietic stem cell transplantation (HSCT)	(39, 50)
Mitochondrial diabetes	Maternally inherited diabetes m.3243A>G mutation in mitochondrial DNA Point mutation in the mitochondrial gene MT-TL1	Rare, not known. Mitochondrial diseases occur in about 1 in 4,000 people.	diabetes and sensorineural hearing loss, myopathy myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	590050	Diet or oral hypoglycemic agents but often require insulin treatment	(7, 40, 41)
Wolfram Syndrome 1	WFS1/AR	1 in 500,000	Neurodegenerative disease is characterized by DM, optic atrophy, diabetes insipidus, and deafness (DIDMOAD). Additional clinical features may include renal abnormalities, ataxia, dementia, or mental retardation	222300	Insulin therapy	(42)

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Rogers syndrome	SLC19A2/ AR	Unknown	Megaloblastic anemia, DM, and sensorineural deafness.	249270	Thiamine and Insulin therapy	(43)

Wolcott-Rallison syndrome, EIF2AK3 gene, Wolcott-Rallison syndrome is a rare autosomal recessive disorder primarily caused by mutations in the EIF2AK3 gene, which encodes the eukaryotic translation initiation factor 2-α kinase 3 (EIF2AK3, also known as PERK or PEK). This syndrome is characterized by PNDM requiring insulin therapy and an early propensity for bone fractures due to skeletal dysplasia. Patients often present developmental delay and growth retardation (37). This condition is particularly prevalent in patients with consanguineous parents, making it the most frequent cause of neonatal or early-onset diabetes in this group. Typically, diabetes is diagnosed before six months of age, and skeletal dysplasia becomes apparent within the first two years of life. Additional clinical manifestations include recurrent episodes of acute liver injury, renal impairment, exocrine pancreas dysfunction, mental retardation, thyroid deficiency, neutrophil defects, frequent infections, and recurrent skeletal fractures. The prognosis for Wolcott-Rallison syndrome is poor, with most patients succumbing to severe hepatitis at an early age (38).

IPEX Syndrome, FOXP3 gene, Immuno-dysregulation, Poly-endocrinopathy, Enteropathy, X-linked (IPEX) syndrome is a rare genetic disorder caused by mutations in the FOXP3 gene. This condition is typically diagnosed within the first year of life and is characterized by autoimmune enteropathy, type 1 DM, and immune system dysfunction. Early manifestations of IPEX syndrome include severe watery diarrhea, eczematous dermatitis, failure to thrive, and growth retardation. The severe immune dysregulation associated with this syndrome can lead to multiple endocrinopathies, autoimmune hemolytic anemia, recurrent infections, and chronic kidney disease. If left untreated, the prognosis for children with IPEX syndrome is poor, with most of them dying in the first two years of life. Early diagnosis and prompt treatment are crucial to improving outcomes for affected individuals (7, 39).

Mitochondrial diabetes, Mitochondrial diabetes should be considered in a child presenting with diabetes and sensorineural hearing loss inherited maternally. This condition is often linked to additional features seen in mitochondrial disorders, such as pigmentary retinopathy, ptosis, cardiomyopathy, myopathy, renal problems, and neuropsychiatric symptoms (40). The most common form of mitochondrial diabetes results from the m.3243A>G mutation in mitochondrial DNA. Children with this condition can initially be managed with dietary changes or oral hypoglycemic agents. However, many will eventually require insulin treatment after a few months or years. It is important to note that metformin is contraindicated in these patients due to the risk of inducing lactic acidosis (41).

Wolfram syndrome, WFS1 gene, Wolfram Syndrome, also known as Diabetes Insipidus, DM, Optic Atrophy, and Deafness (DIDMOAD) syndrome, is an autosomal recessive disorder primarily caused by mutations in the WFS1 gene in approximately 90% of cases. This syndrome is characterized by a combination of several significant clinical features: diabetes insipidus (DI), non-autoimmune insulin-requiring DM as the initial manifestation, progressive bilateral optic atrophy (OA), sensorineural deafness (D), and various neurological symptoms (42). Children with Wolfram Syndrome typically present with DM in early childhood, followed by the development of optic atrophy, which leads to progressive vision loss. Sensorineural deafness also progresses, contributing to significant hearing impairment. Neurological signs may include ataxia, peripheral neuropathy, and psychiatric disorders. The neurodegenerative nature of the condition often leads to a reduced life expectancy, with the average

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age of death being around 30 years, primarily due to neurodegenerative complications (7).

Management of Wolfram Syndrome focuses on symptomatic treatment of the associated clinical conditions. This includes insulin therapy for DM, hormone replacement for diabetes insipidus, and supportive care for vision and hearing loss. Additionally, multidisciplinary care involving endocrinologists, neurologists, ophthalmologists, and audiologists is essential to address the complex needs of these patients and improve their quality of life (7, 42).

Rogers's syndrome, SLC19A2 gene, Rogers's syndrome also known as Thiamine-Responsive Megaloblastic Anemia (TRMA), is characterized by a triad of clinical features including megaloblastic anemia, non-type 1 DM, and sensorineural deafness. This rare autosomal recessive disorder is caused by mutations in the SLC19A2 gene, which encodes a thiamine transporter protein. Patients with TRMA typically present with symptoms of megaloblastic anemia, including hypothermia, lethargy, headaches, pallor, diarrhea, and paresthesia in the hands and feet. Non-type 1 DM manifests as hyperglycemia, often requiring insulin or other hypoglycemic agents. Sensorineural deafness is another hallmark of this syndrome, with onset varying among patients but typically progressing to significant hearing loss. (7, 43). Treatment for Rogers Syndrome involves daily high doses of thiamine (25-75 mg per day). This therapy can significantly improve anemia and may have a positive effect on DM, potentially reducing the need for insulin or other medications. However, the hearing loss associated with TRMA appears to be irreversible and does not respond to thiamine supplementation. Multidisciplinary care, including audiological support and endocrinological monitoring, is essential to address the diverse needs of patients with Rogers Syndrome and to improve their quality of life (43).

Monogenic insulin resistance syndromes (Insulin receptor signaling defect):

There are various forms of MD that result from abnormalities in insulin action, known as inherited insulin resistance syndromes. These syndromes encompass a range of genetic disorders characterized by severe insulin resistance and associated metabolic abnormalities. The clinical features of the more common types of inherited insulin resistance syndromes, including Type A insulin resistance syndrome, Donohue syndrome (leprechaunism), Rabson-Mendenhall syndrome (RMS), and monogenic lipodystrophies, will be discussed here. **(Table 4)** provides a detailed overview of these inherited insulin resistance syndromes.

Type A insulin resistance syndrome, Type A insulin resistance syndrome caused by autosomal dominant mutations in the INSR gene, which encodes the insulin receptor. This syndrome manifests primarily during puberty and is characterized by ovarian hyperandrogenism and acanthosis nigricans. Patients often present with menstrual irregularities such as primary amenorrhea or oligomenorrhea, and many develop polycystic ovarian syndrome (PCOS). Obesity is also a common feature in individuals with this condition (44). The hyperandrogenism associated with Type A insulin resistance syndrome can lead to symptoms such as hirsutism, severe acne, and infertility due to hormonal imbalances. The acanthosis nigricans, a darkening and thickening of the skin in body folds and creases, serves as a visible marker of severe insulin resistance (7, 44). Management of Type A insulin resistance syndrome focuses on reducing insulin resistance and managing diabetes. Treatment typically includes dietary changes aimed at weight reduction and improving insulin sensitivity. Pharmacological interventions involve the use of insulin sensitizers such as metformin and thiazolidinedione (glitazone), which help to decrease insulin resistance and improve glycemic control. In addition to these treatments, managing the symptoms of PCOS is important. This may include hormonal therapies to regulate menstrual cycles and reduce androgen levels, as well as lifestyle modifications to address obesity (7, 44).

Donohue syndrome (leprechaunism) and the Rabson–Mendenhall RMS, Donohue syndrome, also known as leprechaunism, and the Rabson–

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Mendenhall RMS are severe forms of homozygous or compound heterozygous mutations in the INSR gene. Typically, it manifests in infancy with diabetes and robust insulin resistance associated with severe hyperglycemia (45). Donohue syndrome (leprechaunism) is a rare and severe genetic disorder marked by extreme insulin resistance, which impairs the body's ability to use insulin effectively. This condition manifests with significant prenatal growth restriction, leading to very low birth weight and poor postnatal growth. Infants with Donohue syndrome often exhibit hypotonia, which is decreased muscle tone, and developmental delays, affecting motor skills and cognitive functions. Characteristic facial features of Donohue syndrome include large, low-set ears, thick lips, and a flattened nose bridge course (7, 45). Additionally, children with this condition commonly experience organomegaly, which is the abnormal enlargement of organs such as the heart (cardiomegaly), kidneys (nephromegaly), liver (hepatomegaly), spleen (splenomegaly), and ovaries. The prognosis for Donohue syndrome is generally poor, with most affected children succumbing to the disease within the first year of life due to complications from severe metabolic imbalances and organ failure (45). In contrast, Rabson-Mendenhall syndrome (RMS) presents with a milder spectrum of symptoms. Individuals with RMS experience less severe insulin resistance compared to those with Donohue syndrome. Although they may still face challenges related to insulin resistance and metabolic control, children with RMS typically have a longer lifespan and a less severe clinical course (7).

Table 4: The most common phenotypes and genotypes of monogenic insulin resistance syndromes

MD phenotype	Gene / Mode of inheritance	Frequency of cases	Clinical Phenotype	Phenotype MIM number	Treatment	Reference
Type A insulin resistance syndrome	INSR/AD or AR	about 1 in 100,000	DM, insulin-resistant, with acanthosis nigricans and signs of hyperandrogenism	610549	dietary changes and/or drugs (metformin, glitazones) to reduce the insulin resistance	(7, 44)
Donohue syndrome (leprechaunism) and the RMS	INSR/AR	less than 1 per million people	DM, insulin-resistant, with acanthosis nigricans and signs of hyperandrogenism, failure to thrive	246200	Insulin sensitizers Insulin Anti-androgen	(7, 45)
Monogenic Lipodystrophic diabetes	Several different genes: Familial partial lipodystrophy LMNA/ AD Congenital generalized lipodystrophy, type 1 AGPAT2/ AR Congenital generalized lipodystrophy, type 2 BSCL2/ AR	1 in 1 million - 1 in 10 million	Lipoatrophy, insulin resistance, and dyslipidemia, more specifically, hypertriglyceridemia	151660 608594 269700	Diet, Leptin replacement therapy, Insulin therapy, Insulin secretagogues, Metformin, Fibrates and Statins	(46–48)

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Monogenic lipodystrophies diabetes, Monogenic lipodystrophies are a group of rare genetic disorders characterized by a significant reduction or complete absence of adipose tissue. These disorders fall under a heterogeneous category, meaning they present with diverse clinical features but share common metabolic complications, such as severe insulin resistance and hypertriglyceridemia (elevated levels of triglycerides in the blood). The loss of adipose tissue impairs the body's ability to store fat properly, leading to fat accumulation in non-adipose tissues, which contributes to metabolic disturbances (46). The condition is caused by mutations in various genes, each contributing to a different subtype of lipodystrophy, with clinical presentations ranging from mild to severe. Patients with lipodystrophic diabetes often experience profound metabolic challenges, including difficult-to-control diabetes and an increased risk of cardiovascular disease due to high triglyceride levels. Management of lipodystrophy primarily involves dietary interventions. Patients are advised to follow a low-fat diet with a carefully balanced caloric intake to help mitigate metabolic complications. This dietary approach aims to reduce the strain on the body's impaired fat storage mechanisms and improve overall metabolic health (47). In addition to dietary modifications, recent advancements in treatment have introduced recombinant leptin therapy. Leptin is a hormone predominantly produced by adipose tissue, and its deficiency or dysfunction is a key feature in lipodystrophy. Recombinant leptin therapy has shown promising results in clinical trials, demonstrating significant improvements in controlling hypertriglyceridemia and hyperglycemia. This therapy works by supplementing the deficient leptin, thereby improving metabolic regulation, and reducing the risk of complications associated with lipodystrophy (48).

Future Prospects

The future of diagnosing and treating MD holds great promise, driven by advancements in genetic testing, precision medicine, and innovative therapies. As whole genome sequencing and NGS become more available and affordable, earlier and more accurate identification of MD will be possible, allowing for a personalized approach to treatment. This will enable clinicians to distinguish MD from type 1 and type 2 diabetes with better precision, leading to proper therapies tailored to specific genetic mutations. As our understanding of gene function and regulation improves, novel therapies such as gene editing (e.g., CRISPR-Cas9) or gene replacement therapy could potentially correct the defective genes responsible for the disease, offering a curative approach rather than simply managing symptoms.

Strengths

Key strengths of the study lie in tackling the major challenges in diagnosing MD, a disorder often misdiagnosed as type 1 or type 2 diabetes due to its low prevalence, lack of knowledge, and the need for advanced diagnostic tests. Our study emphasizes the importance of improving diagnosis abilities, as less than 10% of individuals with MD receive accurate diagnoses even in developed healthcare systems. The study also highlights how critical a precise diagnosis is for family genetic counseling, permitting more comprehensive screening for further family members with diabetes. The review identifies the higher prevalence of MD in communities with high consanguinity, like Saudi Arabia, and calls for further studies on regional variations in MD incidence.

Limitations

A narrative review of MD has a number of drawbacks, such as the possibility of selection bias and a flaw in the systematic methodology that could result in inaccurate or biased representations of the literature. Subjective and lacking statistical synthesis in narrative reviews raises the possibility of inconsistent study appraisal and author bias; they may limit generalizability and fail to identify research gaps of MD.

Conclusion

MD encompasses various clinical conditions resulting from mutations in a single gene, characterized by early-onset diabetes. These

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conditions include neonatal diabetes, MODY, various diabetes-associated syndromes, and monogenic insulin resistance syndromes. Diagnosis of MD should be considered in diabetic children who do not fit the typical clinical profiles of type 1 or type 2 diabetes, particularly in populations with high rates of consanguinity. For these populations, clinical and laboratory screening for MD is highly recommended. Advances in NGS have made genetic diagnosis more accessible, enabling effective precision medicine for certain types of MD. This approach allows for targeted treatments based on specific genetic mutations, improving management and outcomes for affected individuals.

Disclosures

Author Contributions

The author has reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Ethics Statement

Not applicable.

Data Availability

All data is provided within the manuscript.

Conflict of interest

The author declares no competing interest.

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