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CONGENITAL DIABETES MELLITUS IN NEWBORNS GENETIC ETIOLOGY EARLY DIAGNOSIS AND MODERN THERAPEUTIC APPROACHES

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Abstract. Background: Neonatal diabetes mellitus (NDM) is a rare but clinically significant metabolic disorder characterized by persistent hyperglycemia, insulin deficiency, and impaired glucose homeostasis during early infancy. Unlike conventional type 1 diabetes, neonatal diabetes is predominantly associated with genetic abnormalities affecting pancreatic beta-cell development, insulin secretion, or ATP-sensitive potassium channel function. Early recognition is particularly important because delayed diagnosis may result in severe dehydration, impaired growth, metabolic decompensation, and potentially life-threatening complications.

Objective: This study aims to analyze the genetic and pathophysiological mechanisms, clinical manifestations, diagnostic approaches, and contemporary therapeutic strategies associated with neonatal diabetes mellitus, emphasizing the importance of early genetic testing and individualized treatment.

Materials and Methods: A narrative review of scientific publications and international clinical recommendations was conducted. Relevant evidence was obtained from peer-reviewed research articles, the International Society for Pediatric and Adolescent Diabetes (ISPAD) consensus guidelines, the American Diabetes Association (ADA) Standards of Care, and authoritative clinical genetics resources. The reviewed literature was analyzed using comparative, descriptive, and analytical methods, focusing on molecular pathogenesis, diagnostic criteria, therapeutic effectiveness, and long-term

clinical outcomes.

Results: The literature indicates that approximately 80–85% of diabetes cases diagnosed before six months of age have an identifiable monogenic cause. Genetic abnormalities involving KCNJ11, ABCC8, INS, and the chromosome 6q24 imprinted region are among the important molecular causes of neonatal diabetes. The disease is generally classified into transient and permanent forms, which differ in clinical course, genetic mechanisms, and long-term prognosis. Molecular genetic testing plays a central role in establishing the diagnosis and selecting appropriate treatment. Infants with certain KCNJ11 or ABCC8 variants may respond to oral sulfonylurea therapy, whereas other genetic subtypes require insulin replacement.

Conclusion: Neonatal diabetes mellitus represents a genetically heterogeneous disorder requiring prompt recognition, comprehensive metabolic assessment, molecular genetic diagnosis, and individualized therapeutic management. Integration of genetic testing into neonatal and pediatric endocrine care can improve treatment selection, reduce complications, and support long-term monitoring. Further investigations are needed to clarify genotype–phenotype relationships and evaluate clinical outcomes across different healthcare settings.

Keywords: neonatal diabetes mellitus; congenital diabetes; newborns; monogenic diabetes; KCNJ11; ABCC8; INS; hyperglycemia; genetic testing; insulin therapy; sulfonylureas; pediatric endocrinology.

Introduction

Neonatal diabetes mellitus (NDM) is a rare endocrine and metabolic disorder characterized by the development of diabetes during the first six months of life. The disease is clinically significant because it occurs during a critical period of neonatal growth, metabolic adaptation, pancreatic development, and neurological maturation. Unlike classical autoimmune type 1 diabetes, which generally develops later in childhood, neonatal diabetes is predominantly caused by molecular genetic abnormalities

affecting pancreatic beta-cell function and insulin secretion.

According to the American Diabetes Association Standards of Care in Diabetes—2026, approximately 80–85% of diabetes cases diagnosed before six months of age have an identifiable monogenic etiology. This finding highlights the importance of distinguishing neonatal diabetes from autoimmune diabetes and other causes of hyperglycemia during early infancy.

Literature Review

Neonatal diabetes mellitus (NDM) is a rare and genetically heterogeneous metabolic disorder characterized by the onset of persistent diabetes during the first six months of life. Unlike classical autoimmune type 1 diabetes mellitus, which generally develops later in childhood, neonatal diabetes predominantly results from monogenic abnormalities affecting pancreatic beta-cell development, insulin biosynthesis, or glucose-stimulated insulin secretion.

The scientific understanding of neonatal diabetes has evolved considerably over the past two decades. Earlier investigations primarily focused on clinical manifestations and insulin replacement therapy, whereas contemporary research emphasizes molecular genetic diagnosis, genotype–phenotype relationships, and personalized therapeutic strategies.

The review Neonatal Diabetes Mellitus Around the World: Update 2024 describes important advances in understanding the molecular basis of NDM. The authors reported that more than 40 genes had been implicated in neonatal diabetes by early 2024. This finding demonstrates that NDM represents a heterogeneous group of disorders rather than a single disease entity.

The epidemiological investigation of neonatal diabetes is complicated by its rarity, differences in diagnostic availability, and variations in genetic testing between healthcare systems. Consequently, published incidence estimates vary across populations and study periods.

The increasing recognition of neonatal diabetes has important implications for

neonatal intensive care units, particularly because persistent hyperglycemia in premature or critically ill newborns may initially be attributed to physiological stress, infection, or parenteral glucose administration.

These considerations suggest that improvements in genetic diagnostic accessibility are essential for establishing the true epidemiological burden of neonatal diabetes and identifying affected infants at the earliest possible stage.

Genetic Etiology and Molecular Pathogenesis

The genetic basis of neonatal diabetes represents one of the most extensively investigated aspects of the disorder. Molecular studies have identified multiple pathogenic pathways associated with abnormal pancreatic development, impaired insulin secretion, and beta-cell dysfunction.

Among the most clinically significant genes are KCNJ11, ABCC8, and INS. These genes are involved in the regulation of insulin secretion or synthesis.

The KCNJ11 gene encodes the Kir6.2 subunit of the ATP-sensitive potassium channel, whereas ABCC8 encodes its regulatory SUR1 subunit. Under physiological conditions, increased intracellular ATP concentration following glucose metabolism promotes ATP-sensitive potassium channel closure, pancreatic beta-cell membrane depolarization, calcium influx, and insulin secretion.

Activating pathogenic variants in these genes may prevent appropriate channel closure, resulting in impaired insulin secretion and persistent hyperglycemia.

Trada et al. (2025) reviewed neonatal diabetes associated with ATP-sensitive potassium channel mutations and emphasized the clinical importance of identifying molecular defects before selecting long-term treatment. Their analysis illustrates how genetic diagnosis can directly inform therapeutic decisions.

In contrast, pathogenic variants in the INS gene may impair proinsulin folding and processing, leading to endoplasmic reticulum stress, beta-cell dysfunction, and inadequate insulin production.

Additional genes, including GATA6, EIF2AK3, and FOXP3, may cause neonatal

diabetes as part of complex syndromes involving pancreatic developmental abnormalities, skeletal disorders, immune dysfunction, or other systemic manifestations.

A 2026 review entitled The Genetic Landscape and Precision Medicine in Neonatal Diabetes Mellitus classified major pathogenic mechanisms into ATP-sensitive potassium channel dysfunction, pancreatic developmental defects, and cellular stress-related beta-cell injury. This molecular classification supports the transition from symptom-based treatment toward precision medicine.

Results and Analysis

The analysis of published scientific studies and international clinical recommendations demonstrates that neonatal diabetes mellitus (NDM) is a rare but clinically significant metabolic disorder with considerable genetic heterogeneity. Its early onset, variable clinical manifestations, and potential for severe metabolic complications distinguish it from other forms of childhood diabetes.

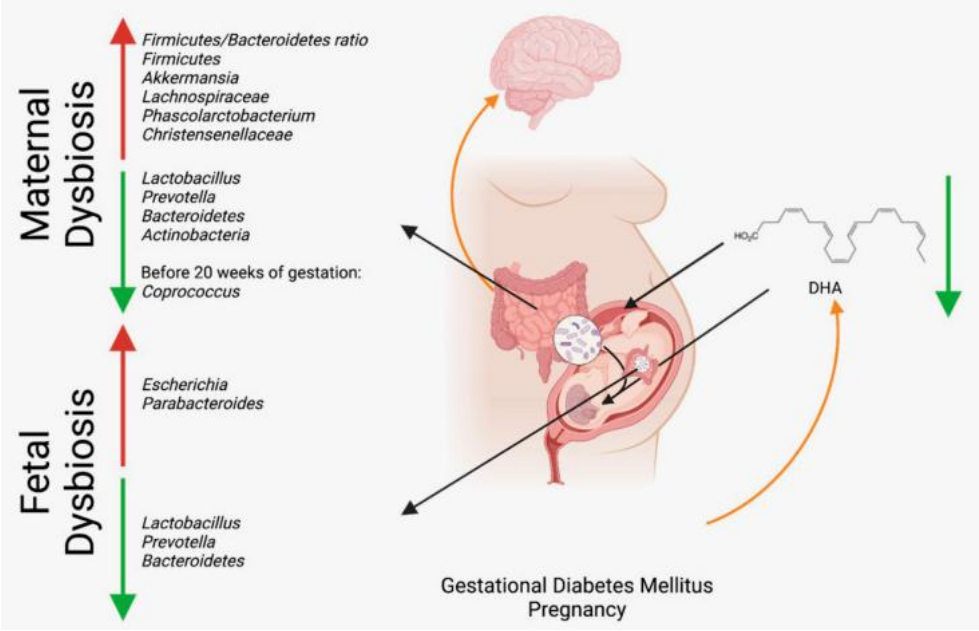

Figure 1. Maternal and Fetal Gut Microbiota Dysbiosis in Gestational Diabetes Mellitus: Potential Mechanisms and the Role of Docosahexaenoic Acid (DHA)

Gestational diabetes mellitus (GDM) is a metabolic disorder characterized by hyperglycemia first recognized during pregnancy that does not meet the diagnostic criteria for overt diabetes. Maternal gut microbiota dysbiosis refers to an imbalance in

the composition, diversity, and functional activity of intestinal microorganisms during pregnancy, potentially contributing to metabolic inflammation, insulin resistance, and altered maternal–fetal metabolic interactions.

Figure 1 illustrates the proposed relationships among maternal gut microbiota dysbiosis, gestational diabetes mellitus, fetal microbial alterations, and docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid.

The diagram highlights changes in the relative abundance of bacterial groups, including Firmicutes, Bacteroidetes, Akkermansia, Lactobacillus, Prevotella, and Escherichia, associated with maternal or fetal dysbiosis. These microbial alterations may contribute to metabolic dysregulation, inflammation, and changes in maternal–fetal interactions.

The figure also identifies DHA as a potentially important nutritional modulator of metabolic and inflammatory pathways. DHA may influence maternal metabolic health and fetal neurodevelopment, although its specific effects on microbiota composition and gestational diabetes outcomes require further investigation.

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines (2022), approximately 80% or more of diabetes cases diagnosed before six months of age have an identifiable monogenic cause. This finding highlights the importance of genetic investigation in newborns and young infants presenting with persistent hyperglycemia.

The reviewed literature further demonstrates that neonatal diabetes is not a uniform clinical entity. It comprises transient neonatal diabetes mellitus (TNDM), permanent neonatal diabetes mellitus (PNDM), and several syndromic forms associated with additional systemic abnormalities.

Clinical classification remains important because the expected disease course differs substantially between transient and permanent forms. However, molecular genetic findings increasingly provide more precise information regarding treatment selection and prognosis.

The analysis identified abnormalities in pancreatic beta-cell development and insulin secretion as the principal molecular mechanisms underlying neonatal diabetes.

The genes KCNJ11, ABCC8, and INS, together with abnormalities involving chromosome 6q24, represent particularly important molecular causes.

1-Table

Analysis of Genetic and Molecular Mechanisms

Genetic abnormality	Pathophysiological mechanism	Clinical significance
KCNJ11	Abnormal ATP-sensitive potassium channel function	Transient or permanent diabetes; potential response to sulfonylureas
ABCC8	Impaired regulation of ATP-sensitive potassium channels	Variable disease course; genotype-dependent therapeutic response
INS	Abnormal insulin biosynthesis or processing	Commonly associated with permanent neonatal diabetes
Chromosome 6q24	Abnormal genomic imprinting and gene expression	Predominantly associated with transient neonatal diabetes
EIF2AK3	Endoplasmic reticulum stress and beta-cell dysfunction	Wolcott–Rallison syndrome and systemic complications
GATA6	Impaired pancreatic development	Diabetes associated with possible congenital abnormalities

The findings indicate that molecular abnormalities influence not only the onset of hyperglycemia but also the clinical course and response to treatment.

ISPAD guidelines identify abnormalities involving chromosome 6q24 as responsible for approximately two-thirds of transient neonatal diabetes cases. Activating variants in KCNJ11 and ABCC8 account for many of the remaining genetically explained cases.

These findings support the clinical importance of molecular classification. In particular, patients with ATP-sensitive potassium channel dysfunction may benefit from genotype-directed pharmacological treatment, whereas infants with impaired insulin biosynthesis frequently require insulin replacement.

The distinction between transient and permanent neonatal diabetes is essential for understanding disease progression, treatment requirements, and long-term prognosis.

2-Table

Comparative Analysis of Transient and Permanent Neonatal Diabetes

Parameter	Transient NDM	Permanent NDM
Typical onset	First weeks or months of life	Usually before six months
Clinical course	Remission during infancy is possible	Persistent diabetes
Common genetic causes	Chromosome 6q24, KCNJ11, ABCC8	KCNJ11, ABCC8, INS, other genes
Treatment	Initially insulin or genotype-directed therapy	Long-term insulin or genotype-directed therapy
Long-term outcome	Risk of recurrence following remission	Continued glucose-lowering treatment required
Genetic testing	Essential	Essential

The comparative analysis demonstrates that clinical remission cannot be interpreted as complete elimination of future diabetes risk.

ISPAD guidelines indicate that approximately half of neonatal diabetes cases require lifelong treatment, while the remaining cases may undergo remission during infancy. Nevertheless, relapse can occur later in life among individuals with transient disease.

Therefore, long-term clinical monitoring remains important even when glycemic abnormalities have resolved.

Clinical Presentation and Diagnostic Challenges

The reviewed studies indicate that the clinical presentation of neonatal diabetes varies according to genetic etiology, severity of insulin deficiency, and associated systemic abnormalities.

Persistent hyperglycemia, dehydration, poor weight gain, and failure to thrive are among the most clinically relevant manifestations. Severe cases may present with diabetic ketoacidosis, requiring urgent medical intervention.

Another important observation concerns intrauterine growth restriction. Insulin plays an important role in fetal growth, and reduced insulin secretion may contribute to low birth weight and small-for-gestational-age status.

The interpretation of neonatal hyperglycemia requires particular caution because

transient elevations in blood glucose may also occur in premature infants, newborns receiving parenteral nutrition, or infants experiencing severe physiological stress.

Consequently, persistent hyperglycemia alone does not establish a diagnosis of monogenic neonatal diabetes.

The evidence supports an integrated diagnostic approach incorporating biochemical assessment, clinical history, evaluation for associated abnormalities, and molecular genetic testing.

The ISPAD recommendation for immediate genetic testing in infants diagnosed with diabetes before six months of age reflects the substantial likelihood of a monogenic etiology in this population.

Conclusion

Neonatal diabetes mellitus (NDM) is a rare, genetically heterogeneous metabolic disorder that presents during the first six months of life and requires early diagnosis, individualized treatment, and long-term clinical monitoring. The present review highlights the substantial progress achieved in understanding the molecular mechanisms, clinical characteristics, and therapeutic management of neonatal diabetes.

The analysis of published scientific evidence demonstrates that approximately 80–85% of diabetes cases diagnosed before six months of age have an identifiable monogenic etiology. Genetic abnormalities involving KCNJ11, ABCC8, INS, and the chromosome 6q24 region play important roles in the development of the disease. These molecular defects influence pancreatic beta-cell function, insulin secretion, clinical manifestations, and treatment responsiveness.

One of the most significant findings is the importance of distinguishing transient neonatal diabetes mellitus from permanent neonatal diabetes mellitus. Although transient forms may undergo spontaneous remission during infancy, recurrence later in life remains possible. Permanent forms generally require continuous glucose-lowering treatment, emphasizing the importance of molecular diagnosis for predicting disease progression and long-term outcomes.

The reviewed clinical evidence also confirms that genetic testing is a fundamental component of neonatal diabetes management. Identification of pathogenic variants enables clinicians to establish a more precise diagnosis, select appropriate therapeutic strategies, and recognize potential neurological or systemic complications.

Particular attention should be given to advances in genotype-directed therapy. Published long-term cohort evidence demonstrates that oral sulfonylureas can provide sustained glycemic control in selected patients with activating KCNJ11 mutations. Nevertheless, treatment effectiveness varies according to the underlying genetic defect, and insulin replacement remains essential for many patients with other molecular subtypes.

Furthermore, the analysis indicates that successful normalization of blood glucose levels does not necessarily eliminate the risk of neurological, developmental, or other systemic complications. Therefore, comprehensive management should integrate metabolic monitoring, neurological assessment, developmental evaluation, and genetic counseling.

From a clinical perspective, persistent hyperglycemia in newborns and young infants should prompt careful differential diagnosis, particularly when accompanied by intrauterine growth restriction, dehydration, inadequate weight gain, or metabolic decompensation. Early collaboration among neonatologists, pediatric endocrinologists, clinical geneticists, and other specialists is essential for improving diagnostic accuracy and treatment selection.

Despite substantial scientific advances, challenges remain regarding the accessibility of molecular genetic testing, the management of rare genetic subtypes, and the availability of long-term follow-up data. Further multicenter and longitudinal investigations are needed to clarify genotype–phenotype relationships, evaluate treatment outcomes, and establish effective diagnostic pathways in different healthcare setting

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