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Type 5 Diabetes: A Distinct Malnutrition-Induced Form of Diabetes Mellitus

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ABSTRACT

Type 5 diabetes, recently recognized by the International Diabetes Federation (IDF), represents a distinct form of diabetes mellitus primarily affecting lean and undernourished individuals in low and middle income countries. Unlike Type 1 and Type 2 diabetes, Type 5 diabetes is characterized by malnutrition induced pancreatic beta-cell dysfunction leading to insufficient insulin production without autoimmune or genetic causes. This review article explores the historical context, pathophysiology, clinical features, diagnosis, treatment approaches, and public health implications of Type 5 diabetes, emphasizing the need for tailored strategies to address this neglected condition.

KEYWORDS

• Type 5 Diabetes • Malnutrition-Related Diabetes Mellitus (MRDM) • Beta-Cell Dysfunction • Insulin Secretion • Nutritional Therapy • Pancreatic Development • Diabetes Classification

INTRODUCTION

Diabetes mellitus has long been classified into well-known categories Type 1, Type 2, gestational, and a handful of rarer forms. However, recent research and global health advocacy have brought to light a previously under recognized form: Type 5 diabetes. Officially recognized by the International Diabetes Federation (IDF) in 2025, Type 5 diabetes is now acknowledged as a distinct clinical entity, especially prevalent among lean, malnourished young people in low and middle-income countries. This review aims to give idea about Type 5 diabetes, including its history, pathophysiology, clinical features, diagnosis, management, and global health implications.[1-3]

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Historical Context and Recognition

Type 5 diabetes is not entirely a new concept. Clinical studies, over 70 years ago, recognized forms of diabetes in under-resources populations that did not seem to represent Type 1 or Type 2 diabetes. For many years, these patients were categorized as Type 1 or Type 2 diabetes and often mismanaged based in inappropriate diabetes classifications, subsequently resulting in poor diabetes outcomes. Only when research was revived, especially by Dr. Meredith Hawkins and his collaborators, that the distinct metabolic characteristics of type 5 diabetes were first described.[1-3]

The IDF created a fundamental turning point in its classification and formal recognition of type 5 diabetes in 2025, followed by a subsequent establishment of a type 5 diabetes working group which recognized the need for appropriate research, criteria for diagnosis, and treatment for an under served population of patients with diabetes.[4]

The Difference between Type 1, Type 2, and Type 5 Diabetes

Feature	Type 1 Diabetes	Type 2 Diabetes	Type 5 Diabetes
Main Problem	Autoimmune destruction	Insulin resistance	Insulin deficiency (not resistant)
Typical Patient	Children, young adults	Adults, often overweight	Lean, malnourished, young adults
Insulin Production	Severely reduced/absent	Normal or high, then low	Reduced, due to pancreatic damage
Insulin Resistance	No	Yes	No
Autoantibodies	Present	Absent	Absent
Prevalence	Worldwide	Worldwide	Low-resource settings, Asia, Africa
Treatment	Insulin	Oral agents, insulin	Often oral agents, rarely insulin

Epidemiology

Type 5 diabetes predominantly affects lean, malnourished adolescents and young adults, especially in South Asia and sub-Saharan Africa. It is estimated to impact millions, though precise figures are lacking due to decades of misdiagnosis and under reporting. The condition is particularly prevalent in regions with high rates of childhood malnutrition and low socioeconomic status.[1-3] Diabetes type 5 is estimated to have a global prevalence of about 25 million people, most situated in both low and middle-income countries, namely India, Sri Lanka, Bangladesh, Uganda, Ethiopia, Rwanda, and Korea. The presentation is mainly in children and young people, simply labeled simply when the body mass index (BMI) is in profile kg/m² less than 18.5, chronic (long-term) under-nutrition.[5]

Pathophysiology of Type 5 Diabetes (Maturity-Onset Diabetes of the Young, MODY 5)

Type 5 diabetes, also known as Maturity-Onset Diabetes of the Young 5 (MODY 5), is a rare monogenic form of diabetes caused by mutations in the hepatocyte nuclear factor-1β (HNF-1β) gene. Unlike type 1 and type 2 diabetes, MODY 5 is inherited in an autosomal dominant pattern and typically manifests before the age of 25. It is characterized by pancreatic β-cell dysfunction, renal abnormalities, and genital tract malformations.[6,7]

Genetic Basis and Molecular Mechanisms

MODY 5 is caused by mutations in the HNF1B gene (located on chromosome 17q12), which encodes the transcription factor HNF-1β. This protein plays a crucial role in:

- Pancreatic β-cell development and function.
- Renal and genitourinary system formation.
- Liver metabolism regulation.

Mutations in HNF-1β lead to defective insulin secretion due to impaired β-cell function rather than insulin resistance.[8] Studies suggest that HNF-1β regulates the expression of genes involved in glucose transport (GLUT2) and insulin secretion pathways.[9]

Pancreatic Dysfunction

HNF-1β mutations result in:

- Reduced insulin secretion due to abnormal β-cell development.

- Impaired glucose sensing, as HNF-1β regulates glucokinase and other glycolytic enzymes.[10]
- Progressive β-cell loss, leading to mild to moderate hyperglycemia.

Renal and Urogenital Manifestations

MODY 5 is strongly associated with renal cysts and diabetes syndrome (RCAD), featuring:

- Renal cysts (multicystic dysplastic kidneys)
- Hypomagnesemia due to impaired renal magnesium reabsorption
- Genital tract malformations (e.g., uterine abnormalities, epididymal cysts).[11]

Clinical Presentation

Patients with MODY 5 often present with:

- Mild fasting hyperglycemia (unlike severe hyperglycemia in type 1 diabetes)
- Low renal threshold for glucose (glycosuria despite near-normal blood glucose)
- Early-onset diabetes (typically before age 25)
- Family history of diabetes in an autosomal dominant pattern.[12]

Moreover, in contrast to Type 2 diabetes, characterized by insulin resistance, Type 5 diabetes involves insulin deficiency, but the person is not insulin resistant. One cause of this disorder is a defect in organogenesis, typically the result of chronic malnutrition beginning in utero and continuing into early childhood.

Some forms of Type 5 diabetes, including MODY 5 (Maturity Onset Diabetes of the Young, Type 5), are caused by single gene mutations that affect beta-cell function in the pancreas. But, the malnutrition-related Type 5 diabetes more recently identified is related to environmental deprivation during nutrient deprivation, specifically lack of protein and/or micronutrients in critical growth periods.

Clinical Features

The key Symptoms for the said disease are as follows:

- Constant fatigue
- Unexplained weight loss or failure to gain weight
- Stunted growth
- Frequent infections
- Excessive thirst and urination
- Poor wound healing
- Digestive problems (e.g., crampy abdominal pain, greasy diarrhea)
- Dark skin patches (acanthosis nigricans)
- Cognitive difficulties (e.g., poor concentration, memory issues)

These symptoms may occur even in the absence of obesity, making the diagnosis easy to overlook in settings where diabetes is typically associated with overweight or older adults.

The associated conditions follow as well:

- Pancreatic insufficiency (leading to digestive symptoms)
- Renal and urogenital anomalies (especially in MODY 5)
- Low birth weight and poor postnatal growth

Diagnosis

Clinical Suspicion

Diagnosis begins with a high index of suspicion in lean, malnourished young individuals presenting with classic diabetes symptoms but lacking features of Type 1 or Type 2 diabetes.

Laboratory Findings

- Elevated blood glucose.
- Low or inappropriately normal insulin levels.
- Absence of autoimmune markers (distinguishing from Type 1 diabetes).
- Absence of significant insulin resistance (distinguishing from Type 2 diabetes).

Genetic Testing

For MODY 5, genetic testing for mutations in the HNF-1β gene confirms the diagnosis. For malnutrition-related Type 5 diabetes, diagnosis is primarily clinical, supported by the history of undernutrition and exclusion of other diabetes types.[13,14]

Management

According to various references, the treatment Strategies for the said disease are as follows.

- **Oral Hypoglycemic Agents:** Many patients can be managed with oral medications such

as sulfonylureas, which stimulate residual pancreatic beta-cell function.

- **Insulin Therapy:** Required only in more severe cases or when oral agents fail.
- **Nutritional Rehabilitation:** Addressing underlying malnutrition is critical for improving pancreatic function and overall health.
- **Enzyme Replacement:** In cases with pancreatic insufficiency, digestive enzyme supplements may be needed.

Novel Therapies

Recent case reports suggest that GLP-1 receptor agonists (e.g., liraglutide) may help regulate glucose metabolism and preserve beta-cell function in MODY 5 patients, allowing for reduced insulin requirements.

Monitoring and Follow-Up

Regular monitoring of blood glucose, growth parameters, and nutritional status is essential. Genetic counseling may be indicated for families with MODY 5.[13]

Prognosis and Complications

Prognosis

With appropriate management, many patients with Type 5 diabetes can achieve good glycemic control and avoid severe complications. However, delayed or incorrect diagnosis can lead to poor growth, recurrent infections, and early-onset diabetes complications.

Complications

- Microvascular complications (retinopathy, nephropathy, neuropathy)
- Poor wound healing and increased infection risk
- Growth failure and developmental delays
- In MODY 5: renal cysts, urogenital anomalies

Global Health Implications

Type 5 diabetes exemplifies the relationship between poverty, malnutrition, and chronic illness. The existence of Type 5 diabetes in settings of limited resources highlights the necessity for public health strategies focused on addressing maternal and child nutrition. The formation of a Type 5 diabetes category by IDF has catalyzed the establishment of working groups to address the issue, along with some research initiatives. This is the beginning of a call for screening, diagnostic, and treatment protocols to consider, and for investment in nutrition and primary care in areas dealing with Type 5 diabetes.

Future Directions

Research Priorities

- Elucidating the full spectrum of genetic and environmental causes
- Developing cost-effective screening tools for low-resource settings
- Studying the long-term outcomes and optimal management strategies
- Integrating nutrition, diabetes care, and social support in health systems

Raising Awareness

Medical education and community outreach are crucial to ensure early recognition and appropriate management of Type 5 diabetes, especially among healthcare providers in high-prevalence regions.

CONCLUSION

Type 5 diabetes represents a long-overlooked but significant form of diabetes, primarily affecting the world's most vulnerable populations. Its recognition as a distinct clinical entity marks a historic shift in global diabetes care, emphasizing the need for equity, tailored interventions, and a renewed focus on the social determinants of health. As research advances and awareness grows, there is hope for improved outcomes and quality of life for millions living with this unique form of diabetes.

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