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Short Communication

Pharmacology Section

An Emerging Form of Diabetes: Type 5 Diabetes Mellitus

MANISHA VARSHNEY[1], JEGAN DURAISWAMY[2], PINAKI PURUSOTTAM[3], SIDDHI PATEL[4]

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INTRODUCTION

The International Diabetes Federation (IDF) at the World Diabetes Congress 2025 in Bangkok, Thailand came up with the new classification of diabetes along with types 1, 2, 3 class (c) and gestational diabetes [1-3]. The IDF has officially recognized Type 5 Diabetes Mellitus (T5DM), formerly known as malnutrition-related diabetes, which was previously overlooked. At the World Diabetes Congress in Bangkok, Thailand, on April 8, 2025, a formal vote was held to confirm this decision, and the IDF approved the new classification. It was an essential step towards the long-ignored condition. The World Health Organisation (WHO) has still not classified it as a distinct category of diabetes due to the lack of proper evidence and diagnostic criteria.

Type 3 Diabetes Mellitus (T3cDM) is a distinct form of the disease caused by existing pancreatic conditions such as pancreatic cancer (ductal adenocarcinoma), cystic fibrosis or haemochromatosis, surgical removal of the pancreas, acute necrotising pancreatitis or congenital absence of the organ (agenesis). While it shares some traits with Type 1 and T1DM, it also possesses its own unique clinical profile [4].

The T5DM was recently found to result from a lack of proper nutrition over a long period. People with this condition deal with a fierce lack of insulin, no ketosis and often live in regions where health care is limited, usually being young adults or lean teenagers. Some scientists propose that people develop Type 1 Diabetes Mellitus (T1DM) due to a lack of nutrients, causing β-cells to disappear and affecting the development of the pancreas. This could be made worse by dysfunctional mitochondria and epigenetic changes [3]. Without a biomarker, physicians currently rely on clinical symptoms (looking youthful, showing undernourishment and needing high levels of insulin) and eliminate other possible causes. Insulin resistance, as seen in T2DM, or autoimmune reactions, as seen in type 1 diabetes, do not cause damage to the pancreas. Rather, it is a non autoimmune form of diabetes that results from the pancreas's incapacity to generate enough insulin because of undeveloped pancreatic tissue [3]. T5DM is listed by the IDF to underscore the major effect worldwide and the urgency to use tailored research and care in the communities at risk [1].

T5DM results from prolonged childhood undernutrition continuing until adulthood that leads to impairment in the development of pancreas. It is hypothesised that correcting the nutritional deficiencies can help to improve symptoms of T5DM. The nutritional deficiencies can be corrected with appropriate nutritional support, providing medications by oral route for stimulating secretion of insulin and if required, low-dose insulin therapy can be initiated [1].

Overview

A form of diabetes which was occurring in thin, young individuals since 1955 with a history of malnutrition from before birth, as well as, during their childhood, has been mentioned in the literature. In the year 1985, WHO classified it as malnutrition related diabetes which was further removed in the year 1999 because this classification lacked scientific evidences, inconclusive follow-up studies and many controversial factors regarding whether undernutrition was a sufficient, direct cause [2,3].

Recent evidence suggests a distinct classification for this diabetes, whose characteristics features are:

- Impairment in insulin secretion from the pancreas;
- Normal peripheral and hepatic sensitivity to insulin;
- Absent ketoacidosis [5-7].

In January 2025, a consensus meeting was held in Vellore, India, where T5DM was proposed as a distinct classification of diabetes. The name was henceforth formally announced by the IDF at the World Diabetes Congress, held in April 2025, where President Peter Schwarz came up with the official launch of the Working Group of T5DM. He was given the task of finding specific diagnostic criteria as well as establishing the guidelines for its treatment [8].

T5DM, known to affect 20-25 million people worldwide, occurs mainly in underweight individuals, who have a history of undernutrition early in life, that continues into adulthood [8]. It is clinically distinct from the Type 1 and T1DM in the sense that T5DM stems from impairment in the development of pancreas which is a consequence of sustained nutritional deprivation during crucial growth periods of childhood and adolescence.

Pathophysiology

While the exact causes still remain unknown but the various reasons which seem to be responsible for the causation of T5DM are:

1. **Impairment in Insulin secretion:** Meredith Hawkins, MD, professor of medicine at Albert Einstein College of Medicine, Bronx, New York, concluded from the findings of her study that there was lower total insulin secretion in the type 5 group than in the other two groups which were T2DM group and lean group without diabetes. She also found that there was higher uptake of glucose and lower production of endogenous glucose in the type 5 group as compared to T1DM group [9,10]. Along with these findings, there was significantly lower lipids and lower visceral adipose tissue in these patients. These findings gave an idea that insulin resistance cannot be the primary reason for malnutrition-associated diabetes. These subjects have an impairment in the development of the pancreas resulting in decreased insulin secretion. These subjects have a defect in their body capacity to secrete insulin [11].
2. **Reduced beta cell function and underdevelopment of pancreas:** Improper nutrition during the intrauterine phase followed by continued undernutrition during the childhood period and adulthood might be the probable reasons for the

insufficient secretion of insulin from the beta cells [9,12,13]. Chronic undernutrition can lead to deficiency of certain antioxidants, eventually leading to impaired functioning of two transcription factors, namely, Pancreatic and Duodenal Homeobox 1 (PDX-1) and V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MafA). This will result in defective beta cell functioning, causing decreased insulin secretion and defective insulin gene expression. The significant increase in Reactive Oxygen Species (ROS) may even lead to apoptosis of beta cell causing defects in insulin secretion [14-16].

3. **Exocrine and endocrine dysfunction of pancreas:** In a previous study done by Bhatia E et al., it was observed that malnutrition-related diabetes patients have diminished pancreatic exocrine and endocrine functions as compared to the control group [17].
4. **No presence of autoantibodies:** In contrast to Type 1 diabetes, historical research shows that malnutrition-related DM patients usually do not exhibit Islet Cell Autoantibodies (ICA), suggesting that autoimmune β-cell destruction is not the mechanism. This supports the idea that Type 5 insulin deficit is non-immune and most likely caused by β-cell functional/developmental insufficiency [1,18].

Metabolic changes and problems affecting the mitochondria are other potential ways by which the disease might develop. In animal model studies, it was seen that limiting protein in early life reduces islet and β-cell numbers and early fasting can interfere with the growth of mitochondria [7,19]. While scientists have not yet worked out the precise genomics of T5DM, epigenetic and grouped genetic factors tied to starvation are assumed to play a major role [7,19]. Although still theoretical here, various authors have proposed that metabolic disorders and neurodegeneration may follow the same pathways (like insulin signalling in the brain [7,19]. Overall, T5DM is mainly characterised by β-cell insufficiency, which is a unique energy-deprivation condition.

Identifying potential T5DM from the presenting symptoms: People with T5DM tend to be underweight, have had childhood nutritional problems and develop the disease during their teen or young adulthood years. Though hyperglycaemia symptoms exist, diabetic ketoacidosis is usually not found. Although patients claim to face no difficulty with ketosis, tests confirm that they have high blood glucose and HbA1c, little useful insulin from their own bodies (with low C-peptide) and high need for extra insulin. Unlike autoimmune type 1, there are no autoantibodies Glutamic Acid Decarboxylase 65 (GAD65) Islet Antigen-2 (IA2) etc., in this type of diabetes. Currently, no reliable genetic or blood tests exist for T5DM, so it must be diagnosed without them [20]. More research is required for the evaluation of diagnostic criteria of this type of diabetes to help understand the exact definition of this particular phenotype.

Global research collaborations to evaluate the diagnostic criteria for this form of diabetes in diverse populations would help refine the definition of this phenotype.

Differentiating features with other types of diabetes:

- People with T5DM do not produce autoantibodies or show ketoacidosis, unlike people with Type 1 diabetes who usually display both.
- People living with T5DM are lean and their insulin sensitivity is high, but people living with T2DM are often heavily overweight and have low insulin sensitivity.
- Young-onset diabetes, which runs in families and is caused by gene mutations, is called Maturity-Onset Diabetes of the Young (MODY). Unfortunately, environmental undernutrition results in T5DM [7].
- Underweight people with insulin-requiring diabetes have pancreatogenic type 3c diabetes, which is often Fibrocalculous Pancreatic Diabetes (FCPD) in the tropics, due to prolonged calcific pancreatitis. Symptoms like abdominal pain, steatorrhea and pancreatic calculus found on scans do not occur in Type 5 but often appear with FCPD. However, as with Type 5, patients with FCPD tend to be lean and only occasionally ketotic, which means one needs to deploy imaging techniques and a history of pancreatitis to distinguish it.
- Many people with maternally inherited diabetes and deafness (MIDD) have hearing loss and maternal inheritance, but these symptoms are rare in traditional T5DM [21].

Treating Difficult Therapeutic Cases

The combination of economic challenges and metabolic disorders encountered in T5DM makes it difficult to find treatments. IDF has assembled a group to design management procedures and rules, but at this stage, there are no established standards. Oral medicine is not strong enough to control diabetes, so insulin is used to treat blood glucose. Considering that people with diabetes often have limited fat stores and reduced energy reserves, doctors should administer insulin slowly and adjust the dose carefully. Many experts suggest reducing insulin requirements by using small doses of insulin in combination with oral medications (such as metformin or sulphonylureas), even though few prospective trials have been conducted [22].

Good nutrition is just as important: supplements with vitamins and quality protein could slowly improve how the body's β-cells function. Care for infections and anaemia must go hand in hand with a nutritional plan. All in all, controlling blood glucose and correcting undernutrition should go hand in hand, which is unlike the other forms of Type 1 diabetes [7].

The clinical importance and usefulness of the results: Public health is greatly affected by T5DM. The group of 20-25 million undernourished people with diabetes has not been a priority in care. Many patients die due to delayed diagnosis and treatment, having endured years of uncertainty. Early detection and distributing resources are major goals of formal classification, which aims to boost awareness among both healthcare professionals and policymakers. By studying T5DM, researchers might finally learn how early-life nutrition shapes beta cells and why that leads to different kinds of diabetes later on. Lastly, it shows that improving global nutrition helps reduce diabetes because it can keep childhood diabetes cases down. Overall, T5DM makes clear a major worldwide problem- a significant metabolic condition caused by a shortage of nutrients rather than overconsumption- and requires unique ways of managing and researching the disease [7].

Critical Analysis of the Proposed Name "Type 5 Diabetes"

There are several concerns regarding the recent suggestion to include malnutrition related diabetes as T5DM by the IDF.

a. Presently, the recognised classification of diabetes is Type 1 diabetes and T1DM. Gestational diabetes is sometimes called as "type 3 diabetes". While other secondary forms due to various medical conditions are included in other categories. Type 3 or Type 4 diabetes has still not been formally recognised by The American Diabetes Association (ADA). An addition of T5DM at this point of time can create confusion.

b. A hierarchical or chronological framework that may not accurately reflect the pathophysiological relevance or clinical significance of these disorders is implied by the use of numerical sequencing in diabetes classification. Proposing any type of diabetes to be "type 5" is premature and could exacerbate already-existing misunderstanding as there are no precise

definitions and worldwide agreement on categories 3 and 4.

c. There are no verified evidence which can demonstrate its aetiopathogenesis [19].

CONCLUSION(S)

T5DM is an emerging form of DM linked to ongoing undernutrition. Even though its cause and metabolism differ from other rare diabetic conditions (those caused by a single gene and those caused by pancreatic problems), there are shared similarities. Doctors should consider diabetes in people from high-risk groups, but only after ruling out a form of diabetes caused by pancreatitis. Treatment involves helping the patient eat the right diet and replacing insulin at the right time. The IDF's official recognition ought to inspire more studies and create personalised advice. The best way to control T5DM is by providing proper nutrition along with diabetes care to improve results for millions. The collaboration between IDF and WHO is required to gather more evidence to highlight this new form of T5DM. Further, extensive studies and research are required to understand the history, occurrence as well as its pathophysiology. Recent evidence suggests that T5DM represents a distinct insulin deficient metabolic phenotype arising from early life undernutrition rather than insulin resistance, carrying major implications for diabetes classification, prevention, and public health policy. Formal recognition of this entity may improve diagnostic accuracy, reduce inappropriate insulin dosing, and promote nutrition-centred treatment strategies, particularly in low and middle income countries where childhood malnutrition remains prevalent. Furthermore, recognition of T5DM highlights the importance of early nutritional interventions across the life course as a preventive strategy against future diabetes burden.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Pharmacology, Dr. D.Y. Patil Medical College Hospital and Research Centre, Pimpri, Pune, Maharashtra, India.
2. Postgraduate Resident, Department of Pharmacology, Dr. D.Y. Patil Medical College Hospital and Research Centre, Pimpri, Pune, Maharashtra, India.
3. Postgraduate Resident, Department of Pharmacology, Dr. D.Y. Patil Medical College Hospital and Research Centre, Pimpri, Pune, Maharashtra, India.
4. Assistant Professor, Department of Pharmacology, Dr. D.Y. Patil Medical College Hospital and Research Centre, Pimpri, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Jegan Duraiswamy,
Postgraduate Resident, Department of Pharmacology, Dr. D.Y. Patil Medical College Hospital and Research Centre, Pimpri, Pune, Maharashtra, India.
E-mail: rjagan946@gmail.com

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