Type 5 Diabetes- The Rejuvenated Spirit from a Ghost of the Past

Diabetes is a less than divine scourge that envelops the planet, by and large induced by an ignominious conglomeration encompassing a multitude of factors involving lifestyle alteration. It transcends socioeconomic boundaries, and its prevalence has skyrocketed worldwide. Ever since the World Health Organisation (WHO) first classified diabetes mellitus (DM) in 1965, the understanding and categorisation of this disease have evolved with multiple paradigm shifts, involving several alterations over a period of the past 3 score years.[1,2] More notably, in 1985, the classification system for diabetes mellitus gained widespread clinical acceptance, introducing a new category: malnutrition-related diabetes mellitus (MRDM).[3] This condition, which was initially noticed in Jamaica and also christened as J-type, K-type, or M-type diabetes, malnutrition diabetes, and ketosis-resistant youth-onset diabetes, had sparked considerable debate due to the lack of scientific evidence, leading to its erasure from the WHO classification in 1999.[4,5] However, the dialogue regarding the presence of MRDM persisted into the current part of the third millennium.

The WHO established specific criteria for diagnosing MRDM, including plasma glucose levels exceeding 200 mg/dl, symptoms of onset under the age of 30 years a BMI below 18.5 kg/m^2, absence of ketosis upon insulin withdrawal, poor socioeconomic status, history of malnutrition, and insulin requirements exceeding 2 IU/kg/d.[3] Samal and Tripathy (1985) identified similar characteristics in patients with diabetes mellitus as described above, including absence of ketosis despite high insulin requirements.[4,5]

Despite a rising BMI and exploding rates of diabetes mellitus, certain parts of the world in Asia, Africa, and Central American countries still report populations with lower BMI, facing a *dual burden of undernutrition*. The lack of a unified nomenclature has led to several patients with MRDM worldwide being under-recognised. A systematic review by Bavuma *et al*.[6] emphasised the need for a common name for lean BMI with diabetes linked to malnutrition, often referred to as atypical forms of diabetes mellitus. Patients with lean BMI and MRDM are often misdiagnosed as having type 1 diabetes, inducing them into a state of long-term basal bolus insulin usage, which could lead to suboptimal treatment. Therefore, establishing a common name for this form of diabetes was imperative for three critical reasons: ensuring a focus on an accurate diagnosis, enabling tailored therapeutic options, and facilitating comprehensive research to deepen our understanding of the disease worldwide and ensuring that there is no patient or physician-related stigma with the continual usage of the word "malnutrition" being attached to a form of diabetes. The Term Type 5 diabetes was introduced during the congress of the international diabetes federation in April 2025, to address a number of these issues.[7]

Patients with Type 5 Diabetes exhibit lean BMI (less than 18.5 kg.m^2)[8] and are diagnosed as young adults, never experience ketosis, originate from low socioeconomic backgrounds, suffer persistent micronutrient deficiencies, possess a structurally normal pancreas, lack a family history of diabetes mellitus, and maintain glycaemic control with oral antidiabetic agents. The differential diagnoses of Type 5 Diabetes encompass type 1 diabetes mellitus,[9] lipodystrophic diabetes mellitus,[10] some forms of monogenic diabetes mellitus,[11] pancreatic and fibrocalcific diabetes mellitus,[12] and certain diabetes related syndromes.

Understanding the pathophysiological mechanisms underlying Type 5 diabetes is critical as it sets this condition apart from other forms of diabetes. Garg *et al*.[13] demonstrated that patients with MRDM from India demonstrated minimal evidence of insulin resistance and did not experience ketosis, unlike those with type 1 diabetes mellitus, as demonstrated with hyperinsulinemic-euglycemic clamp studies (HEC). Suraamornkul *et al*.[14] also used HEC and determined that patients from Thailand, with obesity and type 2 diabetes, had defects in both insulin sensitivity and insulin secretion, whereas lean individuals had only defective insulin secretion. Moreover, these patients had insulin sensitivity similar to that of the healthy controls. Recently, an Indo-American collaboration on patients in India employed advanced stepped pancreatic HEC techniques to explore the metabolic intricacies of atypical low BMI forms of diabetes in Indian males. This research was particularly impactful because it contrasted this unique variant of diabetes not only with traditional forms, such as T1D and T2D, but also with a BMI-matched control group without diabetes.

The experiments revealed that individuals with Type 5 diabetes exhibited a reduced insulin secretory response when compared to both lean BMI normoglycemic controls and the T2DM group. Moreover, endogenous glucose production was found to be lower in patients with Type 5 Diabetes when compared to individuals with T2D. Furthermore, peripheral glucose uptake was significantly higher in patients with lean BMI DM than in those with T2D. Ectopic fat, including visceral adipose tissue and hepatocellular lipids, was extremely low in the Type 5 diabetes group.

The findings from these studies have vitally characterised the understanding of the physiological differences between Type 5 diabetes and T2D.[15]

Conversely, T2D is typically linked to increased glucose production by the liver and markedly reduced glucose uptake in peripheral tissues (reduced 'm' value), neither of which is a significant characteristic of Type 5 DM. The derivations from the 3 HEC studies highlight the fact that type 5 DM appears to differ from T2D. Instead, they primarily have an insulin secretory defect, indicating a dominant beta-cell hypofunction.

The potential mechanisms postulated for this type of diabetes include antioxidant deficiency, persistent undernutrition, and epigenetic modifications.[16,17] More importantly, studies from Jamaica have shown that individuals (aged 17–50 years) who have survived marasmus exhibit lower levels of insulin secretion and greater glucose intolerance than those who have survived kwashiorkor compared to control subjects.[18] Autopsies of stillborn foetuses of subjects with maternal anaemia have demonstrated a significant reduction in the proportion of beta cells when compared to mothers with normal haemoglobin during pregnancy. Moreover, reprogramming of the foetal pancreatic islets, an increase in alpha cells up to 20% higher than in non-anaemic mothers, an increase in non-alpha/beta cells, and an alteration in the alpha-to-beta cell ratio were observed.[19] Brooks *et al*.[20] established reduced beta cells in the pancreas of children who died of protein-energy malnutrition. Early malnutrition or intrauterine growth restriction (IUGR) epigenetically alters PDX1 and thereby β-cell proliferation and insulin gene expression, thereby impairing β-cell response in adulthood.[21]

Experiments in animals corroborate this hypothesis, wherein a long-term low-protein diet significantly reduces both basal and post-glucose-induced insulin secretion when compared with animals fed a normal diet. A study conducted by Khardori *et al*.[22] demonstrated that mice experiencing protein malnutrition in the absence of sepsis or other inflammatory conditions exhibited reduced insulin secretion, carbohydrate intolerance, hepatic dysfunction, and diminished hepatic disposal. These characteristics are analogous with the pathological basis of Type 5 diabetes mellitus in patients with persistent malnutrition from childhood into adulthood.

Furthermore, animals experiencing chronic anaemia during foetal development have also been found to exhibit glucose intolerance. This was demonstrated in foetal sheep, where anaemia was induced, leading to glucose intolerance when compared to healthy sheep without anaemia. This condition was reversed by increasing oxygenation and treating the anaemia. This suggests that undernutrition after birth can result in glucose intolerance.[23] Sanjeevi *et al*.[24] have demonstrated that lean BMI DM in a group of patients who resembled Type 5 diabetes was immunogenetically different from T1D.

There is evidence to show that dysfunction of the incretin axis, which is important for glycaemic homeostasis, and may be impaired in starvation or early-life malnutrition, impairs gut incretin response, thereby modulating expression of signalling molecules such as PAK1 and β-catenin which are responsible for GLP-1 expression and their subsequent secretion from the L cells and into the blood stream.[21]

The Barker hypothesis attributes type 2 diabetes mellitus to individuals born with a lean BMI who later develop type 2 diabetes mellitus owing to excessive nutritional ingestion in infancy and childhood and could face an elevated risk of cardiovascular abnormalities.[25-29] They envisage a situation wherein undernutrition or placental insufficiency occurs in pregnancy, followed by post-natal undernutrition, leading to a reduced beta cell mass, low muscle mass, and wasting[30] – this is the essence of Type 5 Diabetes. However, the precise molecular links between malnutrition and diabetes need more elucidation.[22,31-33] The time has come to delve deeper into this association as understanding it could revolutionise our approach to preventing and managing diabetes.

Within a year or two of epidemiological engineering, solid diagnostic criteria with pointwise weightage will evolve. The medical fraternity would certainly appreciate a canonical representation set in stone. Until then, based on the abundant yet fragmented evidence behind the clinical aspects of this entity, it would suffice to modify the criteria laid down initially by Samal and Tripathy.[5] Regarding patients with a persistently low BMI of less than 18.5 kg/m^2 (The WHO definition of Malnutrition),[34] and having diabetes with a background of undernutrition, particularly those diagnosed with DM before 30 years of age, without a history of *Ketoacidosis* in the past, OR having been diagnosed with "Type 1 DM" and have never had ketoacidosis in the past OR those with Type-1 DM like phenotypes who are on oral antidiabetic agents, this condition should be considered clinically.[9]

They would generally hail from a predominantly rural origin or live in an area with low socioeconomic status or resource-poor areas. If not, it should be considered for those living in an area that is known for frequent drought, famine, war, or natural calamities.[35,36] In general, there is a tendency for evidence of early life undernutrition indicated by one or more of the following features: history of maternal undernutrition, history of low birth weight, birth weight less than the 10th centile for the region of origin of the patient, history of under nutrition in infancy in the form of stunting or wasting OR history of stunting in childhood[36] OR Wasting and/or stunting in adulthood OR history of Stunting among siblings/neighbourhood. These features may coincide with negative clinical signs of insulin resistance (e.g., acanthosis nigricans).[9]

Implementation of diagnostic tools would include, at the very least, a fasting c-peptide level documenting clear-cut beta cell insufficiency (and in more resource-abundant settings, a post-meal c-peptide in addition). At the very least, there is an anti-GAD (glutamic acid decarboxylase) antibody to rule out Type 1 diabetes (most resource-poor settings may struggle to muster this test, leave alone the entire battery).[37]

An ultrasonography of the abdomen (or preferably a CT Abdomen)[38,39] is required to rule out pancreatic diabetes.

A body composition using a DXA Scan[39] or, where DXA is unavailable, using a bioimpedance device in a low-resource area[40] would characterise the very low total body fat, which would, with levels so low, and may only be witnessed in lipodystrophic diabetes mellitus. Patients with monogenic beta cell disease, and particularly those with maturity-onset diabetes of the young Type 5 (MODY 5), which should not be confused with Type 5 diabetes,[41] could be extremely lean—a pedigree chart may help; however, novel variants have been reported on occasion; therefore, a comprehensive next-generation sequencing (NGS) panel may be of value, once again, not something trendy in a resource-poor area.[42-44]

It was demonstrated that around 50% of patients maintained normoglycemia with oral antidiabetic agents alone, without the need for insulin, though this information was determined from a relatively small sample size.[15] Speculation as to whether the introduction of a high protein diet would have a significant impact on improving beta cell function and thereby tempering the clinical nature of the disease would be of interest.[45] Exercise may have an impact on improving lean body (muscle) mass, which could potentially improve the activity of glucose transportation into the periphery.[46]

Further research in terms of studies on both retrospective databases and clinical interventional studies for diet, exercise, and therapeutic agents would be of prime importance in this arena.

In summary, there is an urgent need for the regularisation of the classification of undernutrition-related diabetes and the nomenclature of Type 5 DM, which is being introduced, would help fill in a few lacunae. By addressing this gap, we can enhance our understanding, diagnosis, and treatment of this complex condition, ultimately improve patient outcomes, and advance global diabetes care through meaningful translational and operational research.

Acknowledgements

We acknowledge our partnership with the Albert Einstein College of Medicine, New York and Prof Meredith Hawkins for the academic contribution involved over the years in this arena.

Felix Jebasingh[1,2], Nihal Thomas[1,3]

[1]Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore (CMC), ICMR Collaborating Centre of Excellence, Diabetes, [2]Department of Endocrinology, Austin Health, Melbourne, Australia, [3]Centre for Stem Cell Research (A Unit of InStem Bengaluru), CMC, Vellore, Tamil Nadu, India

Address for correspondence: Dr. Nihal Thomas, Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore (CMC), Tamil Nadu, India.
E-mail: nihal_thomas@yahoo.com

References

1. Diabetes mellitus. Report of a WHO expert committee. World Health Organ Tech Rep Ser 1965;310:1–44.
2. Sreenivasamurthy L. Evolution in diagnosis and classification of diabetes. J Diabetes Mellitus 2021;11:200–7.
3. Diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1985;727:1–113.
4. Ahuja MM, Sharma GP. Serum C-peptide content in nutritional diabetes. Horm Metab Res 1985;17:267–8.
5. Tripathy BB, Kar BC. Observations on clinical patterns of diabetes mellitus in India. Diabetes 1965;14:404–12.
6. Bavuma C, Sahabandu D, Musafiri S, Danquah I, McQuillan R, Wild S. Atypical forms of diabetes mellitus in Africans and other non-European ethnic populations in low- and middle-income countries: A systematic literature review. J Glob Health 2019;9:020401.
7. IDF launches new type 5 diabetes working group. International Diabetes Federation. Available from: https://idf.org/news/new-type-5-diabetes-working-group/. [Last accessed on 2025 Jun 04].
8. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
9. George AM, Jacob AG, Fogelfeld L. Lean diabetes mellitus: An emerging entity in the era of obesity. World J Diabetes 2015;6:613–20.
10. Rajan R, Chapla A, Johnson J, Varghese D, Asha HS, Jebasingh F, *et al*. A series of genetically confirmed congenital lipodystrophy and diabetes in adult southern Indian patients. Sci Rep 2024;14:28277.
11. Chapla A, Mruthyunjaya MD, Asha HS, Varghese D, Varshney M, Vasan SK, *et al*. Maturity onset diabetes of the young in India - A distinctive mutation pattern identified through targeted next-generation sequencing. Clin Endocrinol (Oxf) 2015;82:533–42.
12. Dasgupta R, Naik D, Thomas N. Emerging concepts in the pathogenesis of diabetes in fibrocalculous pancreatic diabetes. J Diabetes 2015;7:754–61.
13. Garg MK, Tripathy D, Shah P. Patients with malnutrition related diabetes mellitus are as insulin sensitive as insulin dependent diabetics. J Assoc Physicians India 1999;47:1145–8.
14. Suraamornkul S, Kwancharoen R, Ovartlarnporn M, Rawdaree P, Bajaj M. Insulin clamp-derived measurements of insulin sensitivity and insulin secretion in lean and obese Asian type 2 diabetic patients. Metab Syndr Relat Disord 2010;8:113-8.
15. Lontchi-Yimagou E, Dasgupta R, Anoop S, Kehlenbrink S, Koppaka S, Goyal A, *et al*. An atypical form of diabetes among individuals with low BMI. Diabetes Care 2022;45:1428–37.
16. Vaiserman AM. Early-life nutritional programming of type 2 diabetes: Experimental and quasi-experimental evidence. Nutrients 2017;9:236.
17. McDonagh M, Ali L, Kahn A, Flatt PR, Barnett YA, Barnett CR. Antioxidant status, oxidative stress and DNA damage in the aetiology of malnutrition related diabetes mellitus. Biochem Soc Trans 1997;25:146S.
18. Francis-Emmanuel PM, Thompson DS, Barnett AT, Osmond C, Byrne CD, Hanson MA, *et al*. Glucose metabolism in adult survivors of severe acute malnutrition. J Clin Endocrinol Metab 2014;99:2233-40.
19. Babu S, Mishra PR, Ravi PK, Swain S, Begum J, Patnaik M. Histomorphogenesis of human pancreatic islets amidst maternal anaemia: a critical insight. Anat Cell Biol 2025. Epub ahead of print.
20. Brooks SE, Golden MH, Payne-Robinson HM. Ultrastructure of the islets of Langerhans in protein-energy malnutrition. West Indian Med J 1993;42:101–6.
21. Chiang YT, Jin T. p21-Activated protein kinases and their emerging roles in glucose homeostasis. Am J Physiol Endocrinol Metab 2014;306:E707-22.
22. Khardori R, Bajaj JS, Deo MG, Bansal DD. Insulin secretion and carbohydrate metabolism in experimental protein malnutrition. J Endocrinol Invest 1980;3:273–8.
23. Benjamin JS, Culpepper CB, Brown LD, Wesolowski SR, Jonker SS, Davis MA, *et al*. Chronic anemic hypoxemia attenuates glucose-stimulated insulin secretion in fetal sheep. Am J Physiol Regul Integr Comp Physiol 2017;312:R492–500.
24. Sanjeevi CB, Kanungo A, Samal KC. Immunogenetic studies on malnutrition-modulated diabetes mellitus. Ann N Y Acad Sci 2002;958:144–7.
25. Jebasingh F, Thomas N. Barker hypothesis and hypertension. Front Public Health 2021;9:767545.
26. Thomas N, Grunnet LG, Poulsen P, Christopher S, Spurgeon R,

Inbakumari M, *et al*. Born with low birth weight in rural Southern India: What are the metabolic consequences 20 years later? Eur J Endocrinol 2012;166:647–55.
27. Barker DJ. The fetal and infant origins of adult disease. BMJ 1990;301:1111.
28. Yajnik CS. Commentary: Thrifty phenotype: 20 years later. Int J Epidemiol 2013;42:1227–9.
29. Ryznar RJ, Phibbs L, Van Winkle LJ. Epigenetic modifications at the center of the Barker hypothesis and their transgenerational implications. Int J Environ Res Public Health 2021;18:12728.
30. Wadivkar P, Thomas N, Jebasingh F, Bacot-Davis VR, Maini R, Hawkins M. Undernutrition-associated diabetes mellitus: Pathophysiology of a global problem. Physiology (Bethesda) 2025. doi: 10.1152/physiol.00065.2024. Epub ahead of print.
31. Ferreira F, Barbosa HCL, Stoppiglia LF, Delghingaro-Augusto V, Pereira EA, Boschero AC, *et al*. Decreased insulin secretion in islets from rats fed a low protein diet is associated with a reduced PKAalpha expression. J Nutr 2004;134:63–7.
32. Reis MA, Carneiro EM, Mello MA, Boschero AC, Saad MJ, Velloso LA. Glucose-induced insulin secretion is impaired and insulin-induced phosphorylation of the insulin receptor and insulin receptor substrate-1 are increased in protein-deficient rats. J Nutr 1997;127:403–10.
33. Heard CR, Turner MR. Glucose tolerance and related factors in dogs fed diets of suboptimal protein value. Diabetes 1967;16:96–107.
34. World Health Organization. Malnutrition in women. Available from: https://www.who.int/data/nutrition/nlis/info/malnutrition-in-women. [Last accessed on 2025 Jun 04].
35. Fonseca VA, Smith H, Kuhadiya N, Leger SM, Yau CL, Reynolds K, *et al*. Impact of a natural disaster on diabetes. Diabetes Care 2009;32:1632–8.
36. Boulton AJM, Jenkins AJ, Makkar B, Mankovsky B, Abera MA, Tesfaye S. Diabetes and natural and man-made disasters: Prevention, preparation, response and recovery. Diabetologia 2025. doi: 10.1007/s00125-025-06406-6. Epub ahead of print.
37. Liepert M, Alhaqqan S, Husain A, Lochnan H, Booth RA, Shaw J, *et al*. The potential of anti-glutamic acid decarboxylase antibodies to support a diagnosis of autoimmune diabetes mellitus. Clin Biochem 2025;135:110842.
38. Wu BU, Lustigova E, Chen Q, Dong EY, Maitra A, Chari ST, *et al*. Imaging of the pancreas in new-onset diabetes: A prospective pilot study. Clin Transl Gastroenterol 2022;13:e00478.
39. Spilseth B, Fogel EL, Toledo FGS, Campbell-Thompson M. Imaging abnormalities of the pancreas in diabetes: Implications for diagnosis and treatment. Curr Opin Gastroenterol 2024;40:381–8.
40. Niewadzi E, Głowińska-Olszewska B, Łuczyński W, Świrydo P, Zduniuk P, Pawelczyk A, *et al*. Analysis of body composition with the use of bioimpedance in children with type 1 diabetes. Pediatr Endocrinol Diabetes Metab 2013;19:58–63.
41. Ge S, Yang M, Cui Y, Wu J, Xu L, Dong J, *et al*. The clinical characteristics and gene mutations of maturity-onset diabetes of the young type 5 in sixty-one patients. Front Endocrinol (Lausanne) 2022;13:911526.
42. Ribeiro AF, Fitas AL, Pires MO, Matoso P, Ligeiro D, Sobral D, *et al*. Whole exome sequencing in children with type 1 diabetes before age 6 years reveals insights into disease heterogeneity. J Diabetes Res 2024;2024:3076895.
43. Kheriji N, Dallali H, Gouiza I, Hechmi M, Mahjoub F, Mrad M, *et al*. Whole-exome sequencing reveals novel variants of monogenic diabetes in Tunisia: Impact on diagnosis and healthcare management. Front Genet 2023;14:1224284.
44. Fareed M, Chauhan W, Fatma R, Din I, Afzal M, Ahmed Z. Next-generation sequencing technologies in diabetes research. Diabetes Epidemiol Manag 2022;7:100097.
45. Longland TM, Oikawa SY, Mitchell CJ, Devries MC, Phillips SM. Higher compared with lower dietary protein during an energy deficit combined with intense exercise promotes greater lean mass gain and fat mass loss: A randomized trial. Am J Clin Nutr 2016;103:738–46.
46. Madsen C, Mogensen P, Thomas N, Christensen DL, Bygbjerg IC, Mohan V, *et al*. Effects of an outdoor bicycle-based intervention in healthy rural Indian men with normal and low birth weight. J Dev Orig Health Dis 2015;6:27–37.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_404_25

How to cite this article: Jebasingh F, Thomas N. Type 5 diabetes - The rejuvenated spirit from a ghost of the past. Indian J Endocr Metab 2025;29:249-52.