Review Article

Beyond Type 1 and 2: A Comprehensive Review of All Types of Diabetes Mellitus

Dr. Virendra Kushwaha*, Dr. Pooja Agrawal, Dr. Mohammad Aamir, Dr Sarthak Goel, Dr. Risabh Gupta
Department of Pharmacology, GSVM Medical College in Kanpur, Uttar Pradesh, India.
***Corresponding author's E-mail:** vkushwaha1970@gmail.com

Received: 06-01-2026; **Revised:** 28-02-2026; **Accepted:** 05-03-2026; **Published online:** 20-03-2026.

ABSTRACT

Diabetes mellitus is a heterogeneous group of metabolic disorders unified by the hallmark feature of chronic hyperglycemia, yet distinguished by varying etiologies, clinical features, and management requirements. While Type 1 and Type 2 diabetes have long dominated clinical focus, a growing body of research has revealed the existence of additional subtypes—each with unique pathophysiological mechanisms and public health implications. The full spectrum of diabetes, including emerging and often under recognized forms such as Latent Autoimmune Diabetes in Adults (LADA), Type 3 Diabetes (brain insulin resistance associated with Alzheimer's disease), Type 4 Diabetes (aging-related insulin resistance in lean individuals), and Type 5 Diabetes or Low BMI Diabetes (previously known as Malnutrition-Related Diabetes Mellitus, MRDM).

Keywords: Diabetes Mellitus, Type 1 Diabetes, Type 2 Diabetes, Latent Autoimmune Diabetes in Adults (LADA), Type 3 Diabetes, Alzheimer's Disease, Type 4 Diabetes, Inflammaging, Senescence-Associated Diabetes, Type 5 Diabetes.

INTRODUCTION

Diabetes mellitus is a complex, chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Once considered a homogeneous disease, diabetes is now recognized as a spectrum of disorders with diverse Pathophysiologies, clinical presentations, and outcomes. Globally, diabetes affects over 463 million people, and this number is projected to rise to 700 million by 2045 [1]. In India, which has been dubbed the "diabetes capital of the world," more than 77 million adults are currently living with diabetes—a figure expected to increase dramatically in the coming decades [2]. Contributing factors include urbanization, sedentary lifestyles, dietary changes, obesity, and genetic susceptibility [3].

Traditionally, diabetes has been categorized into two main types:

• **Type 1 Diabetes (T1D)**: An autoimmune condition, often diagnosed in children or adolescents, where the immune system destroys insulin-producing β-cells in the pancreas, leading to absolute insulin deficiency [4].

• **Type 2 Diabetes (T2D)**: The most prevalent form, usually occurring in adults, marked by insulin resistance and a relative deficiency in insulin production. It is closely linked to obesity and lifestyle factors [5].

However, recent advancements in research have identified several other distinct types of diabetes that challenge the classical classification:

• **Type 1.5 Diabetes (LADA - Latent Autoimmune Diabetes in Adults)**: A hybrid form with features of both T1D and T2D. It typically affects adults who initially do not require insulin but test positive for autoimmune antibodies. Often misdiagnosed as T2D, LADA progresses to insulin dependence over time [6].

• **Type 3 Diabetes**: A proposed term for insulin resistance in the brain, implicated in Alzheimer's disease. It suggests a strong metabolic-neurological connection, where impaired insulin signaling contributes to neurodegeneration[7]

• **Type 4 Diabetes**: An emerging subtype observed in elderly, lean individuals with insulin resistance despite the absence of obesity. It is believed to result from age-related metabolic changes, inflammation, and cellular senescence[8].

• **Type 5 Diabetes: Malnutrition-Related Diabetes Mellitus (MRDM)**

Type 5 Diabetes, commonly referred to as Malnutrition-Related Diabetes Mellitus (MRDM), is a unique and under recognized form of diabetes primarily found in low- and middle-income countries (LMICs). Initially described in 1955 by Hugh-Jones in Jamaica, this condition has since been reported across various LMICs, including India, Bangladesh, Nigeria, Ethiopia, and Uganda[9]. Characterized by a low body mass index (BMI <19 kg/m²), early onset (typically before 30 years of age), a predominantly male prevalence, and absence of ketosis despite severe hyperglycemia, MRDM challenges the conventional classification of diabetes[10].

Patients often require high doses of insulin (>60 IU/day), suggesting significant insulin resistance, though the pathophysiology remains poorly understood[11]. Despite its recognition by the WHO in 1985, MRDM was later removed from official classification in 1999 due to insufficient causal evidence linking malnutrition directly to diabetes[12]. However, recent epidemiological studies from India and Ethiopia continue to report a substantial prevalence of this form—ranging from 6% to 23% of diabetes cases, especially in rural and resource-poor settings[13].

Due to limited access to diagnostic tools, individuals with MRDM are frequently misdiagnosed as having Type 1 Diabetes, leading to potentially inappropriate and overly complex treatment regimens, including unnecessary insulin

therapy. As such, proper metabolic characterization and tailored clinical approaches are essential for effective management of this distinct subtype[14].

In addition to these, several other diabetes forms exist:

• **Gestational Diabetes Mellitus (GDM)**: A form of diabetes first recognized during pregnancy, posing risks to both the mother and the fetus[15].

• **Pancreatogenic Diabetes (Type 3c)**: Caused by pancreatic disorders such as chronic pancreatitis, cystic fibrosis, or pancreatic surgery[16].

• **Drug- or chemically induced diabetes**: From long-term use of glucocorticoids, antipsychotics, or immunosuppressants[17].

• **Syndromic Diabetes**: Associated with genetic disorders like Wolfram syndrome, Down syndrome, or hemochromatosis[18].

The expanding understanding of diabetes subtypes emphasizes the need for precise diagnosis and personalized treatment strategies. Misclassification can lead to suboptimal therapy and increased risk of complications[19].

Table 1: Types of Diabetes

Type	Alternate Name	Key Features
Type 1	Autoimmune Diabetes	Immune-mediated β-cell destruction; insulin-dependent from onset
Type 2	Insulin Resistance Diabetes	Gradual onset; lifestyle and obesity-related; relative insulin deficiency
Type 3	Alzheimer's-related Diabetes	Brain insulin resistance; associated with neurodegeneration
Type 4	Age-related Diabetes	Lean elderly patients; driven by inflammaging and immune dysregulation
Type 5	Syndromic/Malnutrition-related Diabetes	Genetic or nutritional origin; includes MRDM and secondary diabetes
Gestational Diabetes	Pregnancy-induced	Hyperglycemia during pregnancy; increased fetal risk
MODY	Maturity-Onset Diabetes of the Young	Monogenic forms; often misdiagnosed as T1DM or T2DM
LADA	Latent Autoimmune Diabetes in Adults	Autoimmune, slow-progressing; adult-onset, insulin-independent initially
Secondary Diabetes	Drug or disease-induced	Caused by steroids, pancreatic disease, endocrinopathies, etc.

Type 3 Diabetes Mellitus: The Brain's Metabolic Disorder

Introduction

Type 3 Diabetes Mellitus (T3DM) is an emerging concept in which insulin resistance within the brain contributes to Alzheimer's Disease (AD), shifting the view of diabetes beyond systemic metabolic dysfunction to include neurodegenerative processes[20].

Epidemiology and Public Health Relevance

With ~463 million diabetes cases globally in 2019—rising to 700 million by 2045—the growing recognition of T3DM underscores the intersection between metabolic disease and dementia in aging populations[21-.22].

Pathophysiology and Link to Alzheimer's Disease

T3DM features cerebral insulin resistance, impairing neuronal glucose utilization, synaptic function, and promoting neuroinflammation [23-25]. This mirrors hallmarks of AD: amyloid-β accumulation, tau hyperphosphorylation, neuronal loss, and oxidative stress[24,26]. Impaired insulin signaling disrupts LTP, neurotransmitter regulation, and amyloid precursor protein processing via IDE and secretase dysregulation[24].

Glucose Homeostasis and Brain Metabolism

The brain heavily relies on insulin-mediated glucose uptake; cerebral insulin resistance leads to hypometabolism preceding memory decline, implicating astrocyte-neuron glucose transport disruptions.

Mechanisms of Insulin Action in the Brain

Insulin reaches the brain via receptor-mediated transport. Neuronal insulin receptor (IR/IRS-1/IRS-2) signaling through PI3K–AKT and MAPK pathways supports metabolic homeostasis, synaptic plasticity, and neurogenesis. Local brain insulin synthesis, notably in the hypothalamus, has also been suggested[25].

Therapeutic and Diagnostic Implications

Emerging treatments targeting T3DM include:

- **Intranasal insulin**, which improves cognition by restoring insulin signaling.

- **Insulin sensitizers** (metformin, thiazolidinediones), under investigation for neuroprotective benefits.
- **IGF-1 therapy**, aiming to enhance neurotrophic signaling.
  Early detection of brain insulin resistance via markers like p-Ser312-IRS1 may enable timely interventions[26].

Type 4 Diabetes Mellitus: Aging- and Inflammation-Associated Diabetes

Introduction

Type 4 Diabetes Mellitus (T4DM) is a proposed subtype characterized by insulin resistance in lean, elderly individuals. First noted in preclinical models and supported by Salk Institute research, it highlights age-related metabolic changes diverging from traditional T2DM[27,28].

Pathophysiology

Unlike obesity-induced T2DM, T4DM arises from age-related mechanisms:

1. **Inflammaging**—chronic low-grade inflammation impairing insulin signaling.
2. **Senescence-Associated Secretory Phenotype (SASP)**—senescent cells secrete cytokines disrupting metabolic pathways[27,29].
3. **T-cell–mediated inflammation**—without autoantibodies, causing localized insulin resistance[30]
4. **Neurodegeneration link**—shared pathways with T3DM, with cerebral insulin resistance affecting cognition.

Diagnosis

Though no consensus criteria exist, features suggesting T4DM include:

- Age ≥65 years, BMI <25 kg/m²
- Elevated fasting insulin / HOMA-IR with negative diabetes autoantibodies
- Absence of obesity or T2DM family history
- Mild cognitive impairment onset[31]

Investigational biomarkers include IL-6, TNF-α, FDG-PET hypometabolism, and senescence markers.[32]

Therapeutic Management

Management emphasizes a dual neuro-metabolic approach:

1. **Intranasal insulin**—potentially beneficial for cognition
2. **Anti-inflammatory & senolytic agents**—target pathophysiologic drivers[33]
3. **Lifestyle interventions**—exercise and anti-inflammatory dietary patterns
4. **Cognitive monitoring**—using MoCA or MMSE; combined endocrinology/geriatric follow-up.
5. **Precision medicine**—leveraging "omics" and AI for tailored treatment strategies.

Type 5 Diabetes Mellitus: Low BMI Diabetes (LD)

Type 5 Diabetes Mellitus, also known as **Low BMI Diabetes (LD)**, is a distinct, non-autoimmune diabetes phenotype primarily affecting young, underweight individuals in low- and middle-income countries (LMICs)[34]. First described under the term *Malnutrition-Related Diabetes Mellitus (MRDM)* in the 1985 WHO classification, it was later removed in 1999 due to limited pathophysiological clarity. However, recent evidence from metabolic and genetic studies confirms LD as a unique entity with specific diagnostic and therapeutic needs[35,36].

PATHOPHYSIOLOGY

LD exhibits a complex interplay of **nutritional deprivation during early life**, **insulin deficiency**, and **mild insulin resistance**[37]. Key features include:

- **Absence of autoimmune destruction**: Unlike Type 1 Diabetes, LD patients are negative for GAD-65 and IA-2 autoantibodies.
- **No evidence of lipotoxicity or glucotoxicity**: Common in T2D, but not seen in LD due to low adiposity and lack of metabolic syndrome
- **Beta-cell dysfunction**: Impaired insulin secretion due to chronic undernutrition and pancreatic insufficiency [38].
- **Mild peripheral insulin resistance**: Likely arising from altered muscle mass and mitochondrial function[39].

Emerging evidence suggests **epigenetic programming** due to in utero and early childhood malnutrition may impair both **pancreatic development** and **insulin signaling** [40].

Diagnostic Workup

Diagnosis of LD requires a careful **clinical, biochemical, and immunological evaluation** to distinguish it from T1DM and T2DM. Criteria include:

Clinical Features:

- Age < 30 years
- BMI < 19 kg/m²
- Male predominance
- History of undernutrition (childhood or perinatal).
- No episodes of diabetic ketoacidosis (DKA).

Biochemical Markers:

- Fasting C-peptide > 0.5 ng/mL: Suggests preserved beta-cell function

- HbA1c > 6.5% or fasting glucose >126 mg/dL: Diagnostic of diabetes.

Immunological Tests:

- Negative for GAD-65, IA-2, and other autoimmune markers.

Functional Testing:

- Mixed Meal Tolerance Test (MMTT): Reveals blunted insulin response
- Euglycemic-hyperinsulinemic clamp: Demonstrates mild insulin resistance.

Genetic Testing (optional):

- Rule out MODY and lipodystrophy syndromes if clinical suspicion exists[41]

MANAGEMENT

Management of LD differs significantly from T1D and T2D due to its unique physiology:

1. **Nutritional Rehabilitation**:
   - Central to LD management
   - High-calorie, protein-rich diet with micronutrient supplementation (especially zinc, vitamin D, and iron)[42]
   - Address food insecurity and social determinants of malnutrition[43]
2. **Pharmacotherapy**:
   - Oral hypoglycemics (especially insulin secretagogues like sulfonylureas) are often more appropriate than insulin.
   - Metformin may be used cautiously if insulin resistance is present.
   - Avoid early insulin initiation unless absolutely necessary to prevent hypoglycemia in underweight patients.
3. **Avoidance of Insulin Overuse**:
   - Many LD patients are misdiagnosed as T1D and placed on insulin unnecessarily
   - Insulin therapy, if used, should be carefully titrated due to increased hypoglycemia risk.
4. **Regular Monitoring**:
   - HbA1c, weight gain, nutritional status, and C-peptide levels to assess response and adjust therapy.
5. **Education & Support**:
   - Counseling on diet, safe medication use, and recognition of hypoglycemia
   - Public health interventions for prevention of childhood malnutrition may help reduce LD incidence.[43]

CONCLUSION

The classical binary classification of diabetes into Type 1 and Type 2 is no longer sufficient to encapsulate the complexity and diversity of this global health issue. The emergence of additional subtypes—such as LADA, Type 3, Type 4, and Type 5 (Low BMI Diabetes)—underscores the necessity for a more inclusive and precise classification framework. Each subtype presents unique pathophysiological features, diagnostic challenges, and therapeutic requirements that demand individualized clinical approaches.

Low BMI Diabetes, in particular, represents a critical intersection between malnutrition, poverty, and endocrine dysfunction, and is emblematic of the broader need for culturally and socioeconomically sensitive medical paradigms in low-resource settings. Meanwhile, the recognition of Type 3 and Type 4 Diabetes links metabolic disorders with neurodegenerative and age-related processes, respectively, further broadening the clinical implications of diabetes beyond glycemic control alone.

A better understanding of these forms—along with the integration of emerging diagnostic technologies, genetic insights, and biomarker research—will enable clinicians to differentiate between diabetes phenotypes accurately and offer more effective, patient-centered treatment. Moreover, public health strategies must evolve to address the socioeconomic and environmental determinants that influence the development of rarer diabetes subtypes, especially in vulnerable populations.

In conclusion, expanding our knowledge of all types of diabetes is not merely an academic exercise; it is a clinical imperative that can directly influence patient outcomes. Future research should aim to validate diagnostic criteria, explore therapeutic targets, and develop global consensus for a more comprehensive classification. Only then can we hope to fully address the multifaceted burden of diabetes mellitus in the 21st century.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019.
2. Anjana RM, et al. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - Rationale for a national study on diabetes. Indian J Med Res. 2011;133:369–80.
3. Zimmet PZ, et al. Global and societal implications of the diabetes epidemic. Nature. 2001;414(6865):782–7.
4. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet. 2001;358(9277):221–9.
5. DeFronzo RA, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015;1:15019.

6. Naik RG, et al. Latent autoimmune diabetes in adults. J Clin Endocrinol Metab. 2009;94(12):4635–44.
7. de la Monte SM. Insulin resistance and Alzheimer's disease. BMB Rep. 2009;42(8):475–81.
8. Watada H. Type 4 diabetes: a new concept based on age-related insulin resistance. Diabetol Int. 2020;11(3):213–5.
9. Hugh-Jones P. Diabetes in the tropics. Br Med J. 1955;1(4914):648–53.
10. Mohan V, et al. Profile of lean type 2 diabetes in South India. Diabetes Res Clin Pract. 1985;1(4):235–41.
11. Ramachandran A, et al. Diabetes in Asia. Lancet. 2010;375(9712):408–18.
12. WHO Study Group. Diabetes Mellitus. Technical Report Series 727. Geneva: World Health Organization; 1985.
13. Tesfaye F, et al. Prevalence of low BMI diabetes in rural Ethiopia. Diabetologia. 2012;55(1):87–93.
14. Unnikrishnan R, et al. Low BMI diabetes: a clinical conundrum. Diabetes Metab Res Rev. 2019;35(3):e3112.
15. Metzger BE, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002.
16. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c). Curr Diab Rep. 2013;13(6):845–50.
17. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15(5):469–74.
18. Cano A, et al. Syndromic forms of diabetes mellitus. Endocrinol Metab Clin North Am. 2020;49(1):139–61.
19. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2020;43(Suppl 1):S14–31.
20. de la Monte SM. Insulin resistance and Alzheimer's disease. *BMB Rep*. 2009;42(8):475–81.
21. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol*. 2009;66(3):300–5.
22. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.
23. Freiherr J, Hallschmid M, Frey WH, Brünner YF, Chapman CD, Hölscher C, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review. *CNS Drugs*. 2013;27(7):505–14.
24. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. 2018;14(3):168–81.
25. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance. *J Clin Invest*. 2012;122(4):1316–38.
26. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. Impaired insulin and insulin-like growth factor expression and signalling mechanisms in Alzheimer's disease – is this type 3 diabetes? *J Alzheimers Dis*. 2005;7(1):63–80.
27. Seewoodhary J. Type 4 Diabetes Mellitus: A novel hypothesis linking lean elderly individuals with Alzheimer's disease and impaired insulin signaling. *J Gerontol Geriatr Res*. 2021;10(1):1–5.
28. Sadagurski M, White MF. Integrating Metabolism and Aging in the Brain: Potential Roles for sirtuins and insulin/IGF signaling. *Neurobiol Aging*. 2013;34(1):79–88.
29. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14(10):576–90.
30. Chen Y, Zhang J. The role of insulin-degrading enzyme in the clearance of amyloid-beta peptide: implications for Alzheimer's disease. *Ther Clin Risk Manag*. 2007;3(4):589–603.
31. Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, et al. Intranasal insulin improves memory in humans. *Psychoneuroendocrinology*. 2004;29(10):1326–34.
32. Watson GS, Craft S. Insulin resistance, inflammation, and cognition in Alzheimer's Disease: Lessons for multiple sclerosis. *J Neurol Sci*. 2006;245(1–2):21–33.
33. Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiol Aging*. 2006;27(2):190–8.
34. Kalra S, Unnikrishnan AG, Baruah MP, Sahay R. Low BMI diabetes: An emerging entity in the spectrum of diabetes. *J Pak Med Assoc*. 2015;65(9):1009–11.
35. Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. *Curr Diab Rep*. 2013;13(3):435–44.
36. Mohan V, Ranjani H, Unnikrishnan R, Datta M, Anjana RM, Kapoor N. Chronic undernutrition and glucose intolerance in the Indian context: a call for action. *Diabetes Technol Ther*. 2015;17(1):9–14.
37. WHO Study Group. Diabetes mellitus: Report of a WHO Study Group. *World Health Organ Tech Rep Ser*. 1985;(727):1–113.
38. American Diabetes Association. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2023. *Diabetes Care*. 2023;46(Suppl 1):S19–40.
39. Ramachandran A, Snehalatha C, Dharmalingam M. Low BMI diabetes in South India: clinical features and biochemical characteristics. *J Assoc Physicians India*. 2012;60:20–4.
40. Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Toffolo G, et al. Effects of age and sex on postprandial glucose metabolism: differences in insulin sensitivity, secretion, and clearance. *Diabetes*. 2006;55(7):2001–14.
41. Unnikrishnan AG, Kalra S, Purandare V, Baruah MP, Sahay R. Endocrinology in undernutrition: A call to action. *Indian J Endocrinol Metab*. 2016;20(6):856–64.
42. Ranjani H, Kalra S, Mohan V. Emerging pan-Asian phenotypes of diabetes and implications for therapy. *Diabetes Ther*. 2021;12(4):1021–36.
43. Brown AF, Ettner SL, Piette J, Weinberger M, Gregg E, Shapiro MF, et al. Socioeconomic position and health among persons with diabetes mellitus: a conceptual framework and review of the literature. *Epidemiol Rev*. 2004;26(1):63–77.