Diabetology & Metabolic Syndrome

REVIEW

Open Access

Lean type 2 diabetes: the overlooked epidemic reshaping global health

Vinay Singh[1*]

Abstract

Lean type 2 diabetes mellitus an overlooked epidemic emerges as a distinct clinical entity affecting individuals who maintain normal body mass index according to population-adjusted criteria, yet develop diabetes through pathways independent of obesity. This phenotype accounts for 3–8% of global diabetes cases but demonstrates striking regional clustering, with substantially elevated rates across South Asian, Sub-Saharan African, and Caribbean populations. The epidemic's defining characteristics centre on predominant pancreatic β-cell failure rather than classical insulin resistance mechanisms. Affected individuals exhibit compromised insulin production capacity and altered adipose tissue distribution while maintaining seemingly healthy body weights. Paradoxically, clinical outcomes often prove more severe than obesity-associated diabetes, with earlier disease onset and accelerated progression to major complications including cardiovascular disease, nephropathy, and retinopathy. Current healthcare frameworks systematically fail this population through obesity-focused screening algorithms that overlook lean individuals at risk. Diagnostic delays compound the problem, while conventional treatment protocols emphasizing weight reduction prove not only ineffective but potentially harmful. The epidemic remains largely invisible within existing clinical guidelines and public health strategies. This review synthesizes evidence on lean diabetes and T2DM heterogeneity. Observational studies support population-specific risk assessment and β-cell preservation strategies, yet proposed mechanistic distinctions rely on BMI categories rather than standardized measurements of β-cell function or insulin sensitivity. These expert consensus recommendations require randomized trial validation before guideline incorporation. Treatment algorithms should be guided by mechanistic characterization, not BMI alone. Implementation requires consensus measurement thresholds and validation that treatment responses differ by mechanistic phenotype. Systematic investigation may reduce diagnostic delays and advance health equity in vulnerable populations, though clinical implementation depends on generating rigorous controlled trial evidence.

Keywords Lean diabetes, B-cell dysfunction, Precision medicine, Health equity, Population-specific thresholds

*Correspondence:
Vinay Singh
singhvinay001@gmail.com
[1]Department of Medicine, Maulana Azad Medical College, New Delhi, India

Introduction

The conventional understanding of type 2 diabetes mellitus (T2DM) has historically centered on the obesity-hyperinsulinemia model, yet accumulating evidence reveals a critical clinical phenomenon: substantial numbers of T2DM patients present with body mass indices below established overweight thresholds when population-specific criteria are applied [1, 2]. This entity, termed lean type 2 diabetes, transcends regional medical anomalies to represent a fundamental global health challenge that questions obesity-focused diabetes paradigms [3, 4].

Contemporary epidemiological data suggests lean individuals comprise approximately 3–8% of total T2DM cases globally, with marked geographical and ethnic variation in disease burden. The prevalence of the condition is notably elevated in South Asian groups, populations in Sub-Saharan Africa, and communities in the Caribbean. This pattern is thought to arise from the interplay of factors such as early-life nutritional deprivation, inherited susceptibility, and distinctive body composition characteristics that heighten vulnerability [5–7]. For Asian and Pacific Islander populations, lower BMI (Body Mass Index) cut-offs have been recommended, typically 27 kg/m² or 32 kg/m² instead of the conventional 30 kg/m² because research indicates that diabetes risk linked to excess adiposity manifests at comparatively lower BMI levels than those observed in Western populations [8].

Population-based evidence demonstrates the inadequacy of universal BMI thresholds, with a large English cohort study showing Black Caribbean, South Asian, Chinese, and Arab populations developing type 2 diabetes at BMI values 7–13 kg/m² lower than White populations for equivalent risk. South Asians demonstrating diabetes risk at BMI ≥ 23.9 kg/m² comparable to White populations at BMI ≥ 30 kg/m² [9]. Diabetes risk in low and middle-income countries occurs at lower BMI thresholds and younger ages than in high-income settings. Analysis of 685,616 adults across 57 LMICs identified optimal screening thresholds at 23.0 kg/m² for South Asians and 26.0 kg/m² for Black populations substantially lower than the conventional 25.0 kg/m² cutoff. This convergence of lower BMI thresholds with earlier onset creates a distinctive diabetes phenotype that systematically evades detection by screening algorithms calibrated to high-income populations, amplifying health disparities and delaying interventions when β-cell preservation strategies might prove most effective [10].

Major international diabetes organizations have not established distinct clinical frameworks for lean T2DM despite growing epidemiological evidence. The American Diabetes Association's 2025 Standards of Medical Care maintain uniform BMI ≥ 25 kg/m² screening thresholds while recommending earlier screening at age 35, without population-adjusted cutoffs [11]. The 2022 ADA-EASD consensus on hyperglycemia management emphasizes individualization based on cardiovascular and renal comorbidities rather than body composition phenotypes [12]. This gap between observational evidence and guideline implementation reflects ongoing uncertainty regarding diabetes classification approaches.

The clinical importance of lean type 2 diabetes extends beyond classification issues. These patients often experience delayed diagnosis because healthcare providers and patients don't expect diabetes development without visible obesity. This phenotype characteristically presents with pronounced β-cell dysfunction, earlier disease onset, and disproportionately elevated complication risks including cardiovascular disease, nephropathy, and retinopathy despite lower BMI profiles [13]. From a population health perspective, systematic under-recognition perpetuates health disparities in prevention, diagnosis, and treatment, highlighting the critical need to reassess screening approaches, modify clinical guidelines to reflect phenotypic diversity, and expand research addressing population-specific determinants and therapeutic interventions [14].

Lean T2DM consequently represents an underrecognized epidemic requiring fundamental transformation from weight-centric models toward precision medicine frameworks that acknowledge diabetes pathophysiology's heterogeneous nature.

Global BMI-based diagnostic frameworks

Emerging scientific evidence reveals that universal BMI thresholds inadequately assess diabetes risk across diverse ethnic populations, creating systematic underestimation in certain groups while over-estimating vulnerability in others, thereby challenging the validity of standardized body mass classifications in diabetes screening methodologies.

Pacific Island populations

Pacific Islander communities present with distinctively higher lean muscle mass proportions relative to overall body weight, requiring modified diagnostic thresholds where overweight status begins at ≥ 26–27 kg/m² and obesity at ≥ 32 kg/m², establishing lean T2DM parameters as BMI < 26–27 kg/m² with reported prevalence rates under 5% of total diabetes cases [15, 16].

Asian populations

Individuals of South and East Asian descent exhibit enhanced metabolic vulnerability at substantially lower BMI ranges compared to European ancestry populations, with revised international recommendations setting overweight parameters at ≥ 23 kg/m² and obesity at ≥ 25 kg/m², although preliminary investigations suggested even lower thresholds of 19–21 kg/m² prior to

Table 1 Population-Specific BMI thresholds and lean diabetes prevalence

Population/region	Overweight cutoff (kg/m²)	Obesity cutoff (kg/m²)	Lean diabetes definition (kg/m²)	Estimated prevalence
WHO (Universal)	≥ 25	≥ 30	< 25	Variable
Pacific Islanders	≥ 26–27	≥ 32	< 26–27	< 5%
Asians (South/East)	≥ 23	≥ 25	< 23	~ 5–8%
South Asians (India)	≥ 23	≥ 25	< 19–21 (historical), < 23 (contemporary)	~ 3–8%
USA/Western Europe	≥ 25	≥ 30	< 25	~ 5–10%
Africans	≥ 25	≥ 30	< 25 (including ketosis-prone forms)	~ 4–7%
Caribbean	≥ 25	≥ 30	< 25	~ 5%

Table 2 A: regional variations in lean diabetes pathophysiology and clinical characteristics

Region/population	Primary pathophysiology	Clinical characteristics
South & East Asia	β-cell dysfunction; impaired insulin secretion; genetic susceptibility (*TCF7L2*, *HNF1A*)	Younger onset (< 40 years); low BMI; high microvascular complications
Pacific Islands	Primary β-cell insufficiency (rare phenotype)	Familial clustering; occasional MODY-like presentations
Sub-Saharan Africa	Atypical forms including ketosis-prone diabetes	Severe hyperglycemia; recurrent ketosis; transient insulin dependence; frequently misclassified
Caribbean (African descent)	Mixed: insulin deficiency with modest insulin resistance	High complication rates despite lower BMI
Western Countries	Combined β-cell dysfunction and mild insulin resistance	Later presentation; requires LADA evaluation when appropriate

current standardization, establishing lean diabetes criteria as BMI < 23 kg/m² with prevalence ranging 5–8% of regional T2DM cases [17–20].

African populations

Continental African populations generally maintain standard WHO (World Health Organization) classification parameters of ≥ 25 and ≥ 30 kg/m² for overweight and obesity categories respectively, establishing lean diabetes as BMI < 25 kg/m², although complex phenotypic variants such as ketosis-prone diabetes create diagnostic challenges, with lean presentations comprising approximately 4–7% of regional cases [21, 22].

Caribbean populations

Caribbean nations maintain conventional BMI thresholds of ≥ 25 and ≥ 30 kg/m² despite experiencing elevated regional diabetes prevalence, with lean diabetes manifestations documented at approximately 5% across territories including Barbados, Jamaica, and Trinidad [23–26].

Western populations

European and North American populations continue utilizing established WHO criteria, defining lean T2DM as BMI < 25 kg/m² with occurrence rates of 5–10% among diabetes cases, while comprehensive longitudinal analyses from the UK Prospective Diabetes Study and major American cohorts reveal significant lean patient subgroups at diagnosis despite majority overweight presentations, highlighting underlying pathophysiological diversity [27–29].

These collective observations establish that lean T2DM characterization and epidemiological burden demonstrate inherent population specificity, emphasizing the fundamental necessity for customized diagnostic frameworks that appropriately recognize ethnic and regional differences in body composition patterns and diabetes predisposition. As shown in Table 1, population-specific BMI thresholds vary significantly across regions. Notably, South and East Asian populations develop Type 2 diabetes at lower BMI levels compared with Europeans, contributing to a higher prevalence of lean diabetes. These disparities underscore the importance of adopting ethnicity-specific cut-offs for accurate risk assessment.

Pathophysiology and clinical manifestations

Lean type 2 diabetes mellitus exhibits considerable regional diversity in underlying pathophysiological processes and clinical presentation characteristics, reflecting complex interactions between genetic predisposition, environmental influences, and population-specific metabolic profiles.

South and East Asian

These populations demonstrate primary β-cell impairment with compromised insulin secretory function preceding significant insulin resistance development, with genetic variants particularly in *TCF7L2* and *HNF1A* genes substantially contributing to disease susceptibility, typically manifesting before age 40 with disproportionately elevated microvascular complication rates [30, 31].

Pacific Islander

Presentations in Pacific Islander communities predominantly indicate primary β-cell insufficiency with familial aggregation patterns, often resembling maturity-onset diabetes of the young (MODY) phenotypic characteristics [32, 33].

Sub-Saharan African populations

Ketosis-prone diabetes frequently manifests among lean African individuals, characterized by severe hyperglycemic presentations, recurrent ketotic episodes, and intermittent insulin dependency despite absent autoimmune markers, often resulting in inappropriate type 1 diabetes classification [34, 35].

Caribbean populations

Individuals of African descent demonstrate lean T2DM through mixed pathophysiological mechanisms combining insulin deficiency with moderate insulin resistance, presenting with relatively elevated complication rates including retinopathy and nephropathy despite lower BMI profiles, with lean phenotypes representing approximately 5% of regional diabetes cases [36–38].

Western populations

Features in European and North American lean T2DM involves combined β-cell dysfunction with mild insulin resistance, presenting at later onset compared to Asian populations and necessitating clinical evaluation for latent autoimmune diabetes in adults (LADA) when clinically indicated [39–41].

These diverse pathophysiological patterns underscore the necessity for population-specific diagnostic and therapeutic approaches that acknowledge the heterogeneous nature of lean diabetes across different ethnic and geographic contexts. Table 2A illustrates distinct regional patterns in lean diabetes and pathophysiology across global populations. Table 2B outlines three distinct phenotypic subtypes of lean diabetes, each defined by specific measurable criteria.

Table 2 B: proposed measurable phenotyping criteria

Phenotype	Required measurements	Current evidence
Lean + β-cell failure	Fasting C-peptide < 0.8 ng/mL; HOMA-B < 80	Inferred from outcomes; not directly measured
Lean + Central adiposity	Waist circumference > 90 cm (Asian); or visceral fat imaging	Rarely quantified in lean cohorts
Lean + Insulin resistant	HOMA-IR > 2.5	Contradicts assumptions; inadequately characterized

Critical limitation: phenotyping without direct mechanism measurement

The manuscript proposes distinct pathophysiology for lean T2DM (β-cell dysfunction vs. insulin resistance) based on BMI categorization and outcomes, yet lacks direct measurement of these mechanisms. Standard indices remain unmeasured across most lean cohorts: Fasting C-peptide (< 0.8 ng/mL indicates β-cell dysfunction), HOMA-B (β-cell function) and HOMA-IR (insulin resistance) and disposition index (combined reserve and sensitivity assessment) [42–44].

Screening revolution: identifying the invisible population

Ethnicity-specific threshold adaptations

Asian populations, particularly South and East Asian communities, develop type 2 diabetes mellitus at significantly lower BMI values due to increased visceral adiposity prevalence and earlier β-cell failure mechanisms. Consequently, the World Health Organization and regional expert panels recommend reduced overweight thresholds (≥ 23 kg/m²) for these populations [45, 46]. In contrast, Pacific Islander populations demonstrate higher lean muscle mass relative to total body weight, necessitating proposed elevated thresholds (≥ 27–32 kg/m²) to prevent diagnostic misclassification [47].

These population-tailored thresholds extend beyond current International Diabetes Federation positions, which acknowledge ethnic metabolic variations without operationalizing screening modifications [48]. The World Health Organization maintains universal BMI standards while noting Asian populations show diabetes susceptibility at lower values, though this has not yielded revised diagnostic protocols [8]. This implementation gap reflects concerns about diagnostic standardization, potential ethnic stereotyping, and healthcare delivery complexity, though universal thresholds may perpetuate under-identification in vulnerable populations with metabolic dysfunction at lower BMI ranges.

Advanced risk stratification beyond BMI

Exclusive BMI reliance fails to identify individuals with normal-weight diabetes who may harbor significant metabolic risk. Anthropometric measures including waist circumference, waist-to-hip ratio, and advanced imaging-based visceral adiposity assessments provide superior risk discrimination across diverse populations [49, 50]. Recognition of the "metabolically obese normal weight" (MONW) phenotype emphasizes that adipose tissue distribution patterns, rather than total body adiposity, represent primary determinants of diabetes risk [51]. Genome-wide association studies demonstrate that common genetic variants predispose to unfavourable fat distribution despite normal BMI, characterized by

preferential subcutaneous adipose tissue loss with consequent ectopic fat deposition, insulin resistance, and elevated cardiometabolic risk, a polygenic lipodystrophy-like phenotype mirroring monogenic syndromes [52]. Hepatic lipid accumulation particularly mediates diabetes risk in lean individuals, with hepatic steatosis serving as a critical pathophysiological link between adipose dysfunction and metabolic disease independent of total body adiposity [53, 54]. Besides altered distribution of white adipose tissue, ectopic lipid accumulation, particularly in the liver, strongly mediates increased type 2 diabetes risk in lean individuals. Metabolic dysfunction-associated steatotic liver disease (MASLD) frequently occurs in lean T2DM patients, representing a critical link between abnormal fat partitioning and metabolic dysfunction. Heterogeneous patho-mechanisms include impaired adipose tissue expandability, genetic predisposition to hepatic lipid accumulation, and dysregulated hepatokine secretion that collectively disrupt glucose homeostasis [53, 54].

Optimized diagnostic testing strategies

While HbA1c and fasting plasma glucose represent standard screening methodologies, these approaches may systematically underdiagnose diabetes in specific ethnic groups due to hemoglobinopathy prevalence or glycation rate variations [55]. The oral glucose tolerance test (OGTT) maintains superior diagnostic sensitivity, particularly in lean and Asian populations where postprandial hyperglycemia frequently represents the earliest detectable metabolic abnormality [56].

Table 3 Comparative analysis of diabetes screening approaches: Strengths, limitations and Population-Specific applications

Screening approach	Strengths	Limitations	Best-suited populations
BMI-based thresholds	Simple, cost-effective	Misses lean diabetes; inappropriate universal cutoffs	European populations
Ethnicity-specific BMI cutoffs	Adjusted for body composition differences	Remains crude; ignores fat distribution	Asians (≥ 23 kg/m^2), Pacific Islanders (≥ 27–32 kg/m^2)
Waist circumference/WHR	Captures central adiposity; superior risk prediction	Ethnic threshold variation	Asians, populations with central obesity patterns
HbA1c	Standardized, convenient	Ethnic differences require adjustment	Western countries with ethnic adjustment protocols
Oral Glucose Tolerance Test	Most sensitive; detects early postprandial hyperglycemia	Time-intensive, less convenient	Asians, lean phenotypes, normal FPG/HbA1c patients
Genetic risk scores	Identifies pre-onset high-risk individuals	Expensive; limited clinical application	High-risk families, early-onset diabetes
Machine learning-based models	Integrates multiple risk factors; personalized	Requires digital infrastructure	Urban populations with electronic health records

Precision screening innovations

Genomics and digital health technology advances enable ethnicity-tailored risk assessment tool development incorporating family history, lifestyle factors, and metabolic phenotype characteristics. Machine learning algorithms integrating lifestyle, anthropometric, and biochemical markers are increasingly evaluated for their capacity to identify high-risk lean individuals earlier than conventional screening approaches [57, 58].

Policy implementation considerations

Universal BMI-based screening criteria prove inadequate for global diabetes prevention efforts. Adopting ethnicity-specific diagnostic criteria, integrating central adiposity measurements, and expanding OGTT utilization could transform early lean T2DM detection, ultimately reducing diagnostic delays and preventing complications in this systematically underrecognized patient population [10]. Table 3 compares diabetes screening methods across populations. Standard BMI thresholds are simple but miss lean diabetes, suiting European populations best. Ethnicity-specific BMI cutoffs (≥ 23 kg/m² for Asians, ≥ 27–32 kg/m² for Pacific Islanders) address body composition differences but ignore fat distribution. Waist measurements capture central adiposity with superior risk prediction for Asian and centrally obese populations despite requiring ethnic-specific thresholds.

Implementing mechanistic measurement

Clinical screening should progress beyond anthropometrics to include:

- **Fasting C-peptide** (>200 pmol/L = reasonable reserve; <100 pmol/L = dysfunction) [59].
- **HOMA indices** (calculate from fasting glucose + insulin) [60].
- **Proinsulin-to-insulin ratio** (elevated in early β-cell failure) [61].

Several barriers impede widespread implementation. Fasting insulin measurements are not routinely available in resource-limited settings, reference ranges lack standardization across populations, and assay variability affects clinical interpretability. The development of simplified point-of-care biomarkers is essential to overcome these challenges.

Management paradigm: beyond weight-centric approaches

Inadequacy of conventional weight-focused strategies Standard diabetes management emphasizing weight reduction proves inadequate for lean type 2 diabetes mellitus, where β-cell dysfunction rather than excess adiposity drives hyperglycemia [62, 63].

Modified lifestyle intervention strategies Therapeutic objectives in lean diabetes management require a fundamental shift from conventional weight loss goals to preserving lean muscle mass, enhancing insulin sensitivity through structured physical activity, and targeting visceral adiposity reduction [64–67]. Mediterranean-style dietary patterns and low-glycemic index nutritional approaches provide significant metabolic advantages without necessitating substantial weight reduction. Exercise prescriptions should emphasize resistance training combined with moderate-intensity aerobic activities to maintain muscle mass and improve insulin sensitivity rather than focusing on aggressive caloric expenditure for weight loss purposes.

Pharmacological treatment optimization Although metformin retains its first-line therapeutic status, its clinical effectiveness may be compromised in lean diabetes patients who lack the obesity-driven insulin resistance typically targeted by this medication [68]. GLP-1 receptor agonists may benefit lean patients with demonstrated β-cell dysfunction (fasting C-peptide < 0.8 ng/mL or HOMA-B < 80), though RCTs specifically testing this in lean cohorts are absent [69]. SGLT2 inhibitors may benefit those with documented visceral adiposity (waist circumference >90 cm for Asians), though comparative effectiveness by body composition remains unstudied. Early insulin should be considered when β-cell reserve is formally assessed as severely compromised, though the threshold distinguishing 'severe' from 'moderate' dysfunction in lean versus obese individuals is undefined [70].
Early insulin therapy initiation frequently becomes essential for patients presenting with significant β-cell dysfunction, reflecting the distinct pathophysiological profile of lean diabetes compared to obesity-associated disease variants [71].

Precision medicine integration Molecular characterization through genetic testing and metabolomic profiling enables identification of distinct lean T2DM phenotypes requiring tailored therapeutic interventions [72, 73]. Treatment algorithms should differentiate between patients with predominant insulin deficiency, who achieve optimal outcomes through early insulin therapy initiation, and those presenting with visceral adiposity patterns, who demonstrate favorable responses to lifestyle modifications combined with SGLT2 inhibitor therapy targeting their specific pathophysiological mechanisms.

Clinical and policy implications The transition from standardized, weight-centered treatment guidelines toward phenotype-driven, precision-based management approaches holds significant potential for preventing complications and improving outcomes in this systematically underrecognized diabetes subgroup [12]. Figure 1 describes a streamlined approach to lean T2DM management that begins with diagnosis, lifestyle interventions, insulin therapy, tailored and precision approach.

Comparison with current treatment guidelines International diabetes guidelines do not stratify treatment by BMI phenotype. The 2022 ADA-EASD consensus prioritizes therapy selection based on cardiovascular disease, heart failure, and chronic kidney disease, with glucose-lowering efficacy and weight as secondary considerations [12]. This patient-centered framework does not address potentially distinct pathophysiological mechanisms in lean versus obese T2DM.

The Endocrine Society lacks lean diabetes-specific guidelines, and the 2020 ADA-EASD Precision Medicine Consensus recognizes phenotypic variation requiring individualization without establishing BMI-differentiated protocols [74]. Therefore, our proposed approach emphasizing β-cell preservation, earlier insulin consideration, and reduced weight-reduction focus represents expert interpretation of observational data rather than established guidelines. This underscores the need for randomized trials specifically enrolling lean T2DM patients to generate evidence-based protocols.

Clinical outcomes and prognosis

The paradox of lean diabetes outcomes Lean type 2 diabetes mellitus demonstrates counterintuitive clinical outcomes compared to obesity-associated diabetes. Despite lower BMI and occasionally more favourable lipid profiles, these patients often experience equivalent or worse cardiometabolic outcomes [75, 76].

The obesity paradox in diabetes care Epidemiological evidence demonstrates elevated mortality risk among lean diabetic patients compared to their overweight counterparts, highlighting the paradoxical protective effect of obesity in diabetes outcomes [77–79]. While often attributed to predominant β-cell dysfunction in lean individuals, this explanation lacks strong data support. Alternative explanations include severe insulin resistance as the primary defect, more aggressive underlying metabolic dysfunction, unrecognized comorbidities, or diagnostic delays. The true mechanisms underlying the obesity paradox remain incompletely understood and require pro-

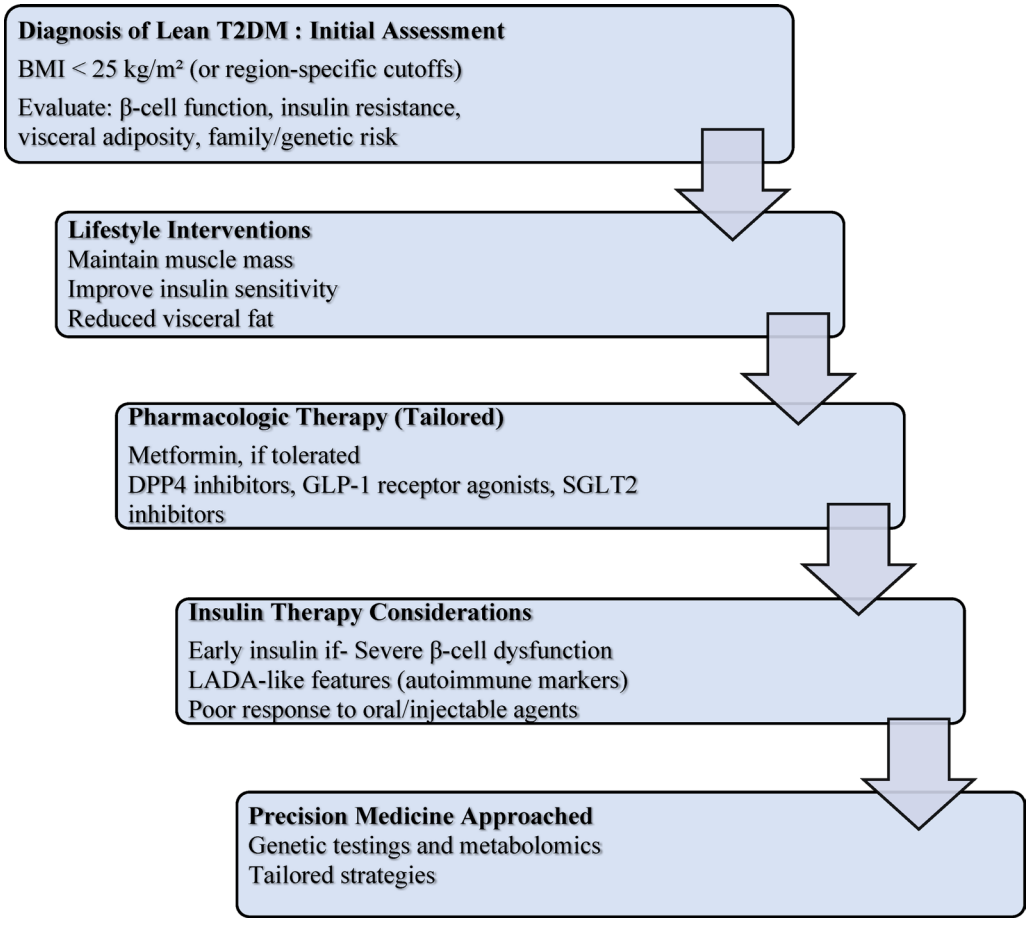

Fig. 1 Management of Lean Type 2 Diabetes Mellitus (T2DM)

spective studies comprehensively characterizing insulin secretion, insulin sensitivity, and clinical outcomes across BMI categories.

Major cardiovascular outcome trials informing current diabetes treatment (EMPA-REG OUTCOME, LEADER, CANVAS, DECLARE-TIMI predominantly enrolled overweight and obese participants, limiting generalizability to lean phenotypes [80–82]. Current ADA Standards acknowledge this limitation but provide no lean-specific modifications, recommending cardioprotective agents (SGLT2 inhibitors, GLP-1 receptor agonists) based on comorbidities rather than body composition [11]. Whether increased lean diabetic mortality reflects distinct disease biology or methodological confounding remains unresolved without BMI-stratified trials with comprehensive metabolic characterization.

Complication profiles Cohort studies reveal elevated incidence rates of microvascular complications, particularly diabetic retinopathy and nephropathy, among lean T2DM patients, likely resulting from delayed diagnosis and insufficient screening protocols [83, 84].

Regional outcome variations Prognosis demonstrates significant geographic variation. In Asian and African populations, lean T2DM patients often present with advanced complications and encounter limited therapeutic resource availability [85]. In Western healthcare systems, while treatment accessibility improves, misclassification as type 1 diabetes or LADA frequently delays optimal interventions [86]. Table 4 shows outcome comparison between lean versus obese type 2 diabetes. These are observations which are weakly supported by data and which need confirmation in large clinical studies.

Health system implications

Current system inadequacies Healthcare systems developed around obesity-driven diabetes models inadequately address lean T2DM, particularly in resource-constrained environments [87].

Screening program transformation Current BMI-centric screening protocols systematically fail to identify lean diabetes cases in high-prevalence populations, necessitating adoption of ethnicity-specific diagnostic thresholds and comprehensive anthropometric evaluations to sub-

Table 4 Outcomes Comparison - Lean versus obese type 2 diabetes

Outcome domain	Lean T2DM	Obese T2DM
Cardiovascular disease risk	Equal or elevated risk despite lower BMI	Elevated risk primarily from obesity-related factors
Glycemic durability	Accelerated β-cell failure; earlier insulin requirements	Extended glycemic control with oral agents
All-cause mortality	Higher mortality in multiple cohorts ("obesity paradox")	Lower mortality in overweight compared to lean diabetics
Microvascular complications	Higher risk in some studies due to diagnostic delays	Risk strongly associated with obesity, hypertension, duration
Hypertension & dyslipidemia	Less frequent; sometimes more favorable metabolic profile	More common; primary cardiovascular risk driver
Diagnostic classification	Frequently misdiagnosed as type 1 diabetes or LADA	Usually correctly identified as T2DM

stantially enhance detection capabilities [88–90]. Screening frameworks must integrate metabolic health status as a critical risk stratification tool beyond traditional anthropometric measures. Metabolic health characterized by absence of hypertension, dyslipidemia, hyperglycemia, and elevated inflammatory markers provides superior diabetes risk discrimination compared to BMI alone, particularly for identifying high-risk lean individuals [91].

Clinical guideline modernization Current treatment guidelines emphasizing weight reduction require fundamental revision to address distinct management requirements of lean T2DM, with therapeutic priorities redirected toward β-cell preservation and cardiovascular risk mitigation rather than conventional weight-based interventions [92]. Clinical diagnostic algorithms must integrate specific lean diabetes recognition criteria to prevent patient misclassification and ensure appropriate treatment protocol selection, thereby avoiding application of obesity-focused therapeutic approaches that may be ineffective or potentially harmful in this patient population.

Absence of lean-specific guidelines reflects both insufficient trial evidence and conceptual frameworks viewing T2DM as a pathophysiological continuum rather than discrete subtypes. The 2020 Precision Medicine Consensus advocates data-informed phenotyping while noting that implementation requires validated biomarkers, treatment-responsive classifications, and demonstrated clinical utility—criteria not yet met for lean T2DM [73]. Concerns about creating artificial distinctions without biological validation must be weighed against potential benefits of targeted approaches. These factors explain guideline conservatism while highlighting needs for mechanistic research determining whether lean T2DM represents a biologically distinct entity or lower-BMI manifestation of heterogeneous T2DM pathophysiology.

Healthcare provider education Primary care training programs require comprehensive enhancement to incorporate lean diabetes recognition principles, underlying pathophysiology, and appropriate management strategies into clinical education curricula [93, 94]. Random non-fasting C-peptide testing (< 200 pmol/L indicating significant β-cell dysfunction) may assist in differentiating lean T2DM from LADA in diagnostically uncertain presentations where autoimmune diabetes is suspected [95]. However, practical implementation barriers—including laboratory requirements, interpretation challenges, and limited availability in primary care restrict routine use, particularly in resource-limited settings.

Policy development priorities From a policy development perspective, lean T2DM highlights fundamental limitations of standardized global strategies. International health organizations and national health authorities must adopt population-specific BMI thresholds for screening and diagnostic purposes, similar to WHO's ethnicity-adjusted BMI recommendations for Asian populations [9]. Furthermore, targeted investment in diabetes registry systems and real-world data collection initiatives can better quantify the true burden of lean diabetes, informing evidence-based policy decisions and healthcare resource planning [96].

Research priorities

Epidemiological research needs Population-based prevalence studies across ethnic populations remain inadequate, requiring large-scale multiethnic cohort investigations to establish precise prevalence estimates by demographic and geographic variables [97, 98]. Longitudinal studies tracking disease progression from prediabetes through complications in lean individuals are essential for developing evidence-based prevention strategies and informing optimal treatment timing.

Mechanistic research imperatives Etiological pathways underlying lean diabetes require investigation through genomic, metabolomic, and epigenetic methodologies to distinguish mechanisms from obesity-associated diabetes [99, 100]. Advanced β-cell function assessment techniques must be developed to improve risk prediction and optimize treatment selection in lean patients.

Screening innovation Advanced screening strategies must extend beyond universal BMI thresholds to incorporate waist circumference, metabolic health parameters, and body composition assessments for identifying high-

risk lean individuals who warrant diagnostic glucose testing ([101]– [102]). Point-of-care technologies suitable for resource-limited settings remain essential for equitable implementation in populations where lean T2DM prevalence is highest.

Therapeutic research Randomized controlled trials specifically enrolling lean T2DM patients represent an urgent priority, as existing recommendations inappropriately extrapolate findings from obese populations [95, 96]. Comparative effectiveness studies between lean and obese diabetes cohorts are essential for establishing evidence-based treatment selection criteria.

Health systems research Implementation science studies evaluating screening effectiveness, healthcare preparedness, and cost-effectiveness for lean diabetes remain absent [103]. Comprehensive diabetes registries capturing BMI-stratified outcomes and disease progression data would provide evidence foundations for policy development and resource allocation decisions.

Guideline development research: Establishing lean T2DM-specific guidelines requires resolving key questions: [1] Does lean T2DM represent a distinct pathophysiological entity warranting independent classification [2]? Do treatment responses differ sufficiently by BMI to justify stratified algorithms [3]? What barriers prevent ethnic-specific screening threshold adoption despite epidemiological support?

Addressing these requires prospective studies with standardized lean T2DM definitions, detailed metabolic phenotyping (insulin secretion and sensitivity, body composition imaging), and comparative treatment trials. Only through such evidence can proposals advance from expert interpretation to guideline endorsement by international organizations (ADA, EASD, IDF, Endocrine Society). Current guideline absence reflects insufficient controlled trial evidence rather than dismissal of lean T2DM's clinical significance.

Knowledge gaps

Absence of dedicated randomized controlled trials Lean T2DM patients have never been specifically enrolled in RCTs. Treatment guidelines inappropriately apply findings from obesity-predominant trials, leaving optimal pharmacotherapy and insulin initiation timing unvalidated for this population.

Lack of longitudinal natural history data Progression trajectories from prediabetes to complications remain unmapped in lean individuals. Critical unknowns include β-cell decline kinetics, complication emergence timing, and disease velocity relative to obese phenotypes.

Inadequate mechanistic phenotyping Fundamental pathophysiology relative importance of β-cell failure versus insulin resistance, genetic versus environmental contributions, nosological status within T2DM requires genomic, metabolomic, and epigenetic characterization currently absent from literature.

Body composition assessment gaps BMI cannot measure visceral fat, ectopic lipid accumulation, or lean tissue mass the actual determinants of metabolic risk. Clinically feasible, standardized tools for fat distribution assessment await development and validation.

Unresolved obesity paradox mechanisms Excess mortality in lean versus obese diabetics defies explanation. β-cell dysfunction is invoked without robust evidence; competing hypotheses (primary insulin resistance, diagnostic lag, hidden comorbidities) need prospective investigation with detailed metabolic characterization.

Absent β-cell function assessment standardization Practical, validated methods to quantify pancreatic reserve don't exist clinically. C-peptide testing faces implementation obstacles; sophisticated techniques for detecting early secretory decline and guiding therapy remain experimental.

Implementation science vacuum Evidence on real-world screening program effectiveness, health system preparedness, clinician education requirements, and service delivery optimization is non-existent. Translation of ethnicity-specific screening from theory to practice lacks empirical foundation.

Missing health economic evaluation Population-tailored screening, early treatment intensification, and phenotype-specific interventions have undergone no cost-effectiveness analysis. Decision-makers in high-burden, resource-limited nations lack economic justification for implementation.

Absence of standardized mechanistic measurement protocols Literature uses disparate C-peptide thresholds (0.8–1.5 ng/mL), heterogeneous HOMA calculations, and variable hepatic steatosis assessments. International consensus on measurement standards is prerequisite for phenotype definition, treatment algorithm development, and cross-study comparison.

Areas of controversy

Distinct entity or part of the T2DM spectrum Controversy exists whether lean T2DM is a separate disease or the lower BMI end of T2DM. Distinct classification advocates cite predominant β-cell failure, earlier onset, and

worse outcomes warranting dedicated guidelines. The spectrum view argues for continuous pathophysiological variation across BMI favoring integrated management. This impacts treatment protocols and research priorities.

Population-specific vs. universal BMI thresholds Debate surrounds ethnicity-adjusted BMI cutoffs. Critics cite diagnostic inconsistency, research comparison difficulties, and potential ethnic stereotyping. Advocates argue universal thresholds miss high-risk populations and worsen health disparities.

Primary defect: β-cell dysfunction vs. insulin resistance: Despite widespread attribution to β-cell failure, data support remains limited. Alternative theories propose primary insulin resistance with inadequate compensation. This mechanistic ambiguity directly affects treatment choice: insulin secretagogues, sensitizers, or early insulin therapy.

Obesity paradox interpretation Higher lean diabetic mortality lacks consensus explanation. Competing hypotheses include intrinsically aggressive pathophysiology, diagnostic delays causing lead-time bias, confounding from comorbidities inducing weight loss, or reverse causation. Each mechanism implies different intervention strategies.

LADA overlap and diagnostic boundaries Differentiating lean T2DM from LADA and ketosis-prone diabetes remains problematic. Unstandardized autoantibody protocols and inconsistent C-peptide thresholds create diagnostic uncertainty affecting immunotherapy consideration and insulin timing decisions.

Metformin first-line status in lean patients Metformin's effectiveness in lean diabetes—where insulin resistance may be minimal is questioned. Some advocate early incretin therapies or insulin targeting β-cell dysfunction; others emphasize metformin's benefits beyond insulin sensitization. Evidence-based resolution remains elusive.

Screening strategy cost-effectiveness Population-specific screening programs face scrutiny. Critics challenge costs of ethnicity-tailored infrastructure, training, and testing requirements. Proponents argue universal approaches miss cases, generating higher long-term complication costs.

Terminology and stigma "Lean diabetes" terminology itself provokes debate. Critics suggest it inappropriately pathologizes normal weight and risks metabolic complacency. Alternative terms (normal-weight diabetes, BMI-stratified subtypes) lack consensus, hampering clinical communication and disease recognition.

Future directions

Precision medicine implementation Future diabetes care demands precision medicine integration through ethnicity-specific diagnostics, advanced body composition analysis, and comprehensive biomarker screening for early lean diabetes detection [104, 105]. Artificial intelligence and digital health platforms must incorporate non-traditional risk factors into clinical workflows to identify overlooked high-risk lean individuals.

Individualized treatment paradigms Lean T2DM's primary β-cell dysfunction requires pathophysiology-driven algorithms emphasizing early insulin therapy, incretin treatments, and β-cell preservation over weight-focused interventions [106, 107]. Personalized protocols utilizing genetic testing, metabolomic profiling, and clinical phenotyping must guide individualized therapeutic decisions.

Health system transformation Lean diabetes-specific care pathways must integrate targeted screening, specialized nutrition support, and systematic complication monitoring to bridge current care gaps [108]. Concurrent provider education programs focusing on lean diabetes recognition and management are essential for improving care quality in this underserved population.

Global health equity High-prevalence low- and middle-income countries require prioritized international funding and collaborative research initiatives to address lean diabetes disparities [109]. BMI-stratified registries and lean diabetes integration into national guidelines will establish systematic frameworks for equitable healthcare delivery.

Public health communication Public health campaigns must move beyond the conventional diabetes-obesity paradigm to embrace the multifaceted nature of diabetes while fostering comprehensive prevention approaches [110]. Community-focused educational initiatives in high-burden regions will strengthen symptom awareness and healthcare engagement among diverse at-risk groups who fall outside conventional diabetes stereotypes.

Lean type 2 diabetes mellitus exposes the limitations of a one-size-fits-all approach to diabetes care. Moving forward, research, practice, and policy must converge to create precision medicine frameworks that account for heterogeneity in clinical presentation, pathophysiology, and prognosis. Figure 2 shows a conceptual roadmap illustrating priority areas for advancing lean type 2 diabetes management.

Limitations

This review acknowledges several important limitations:

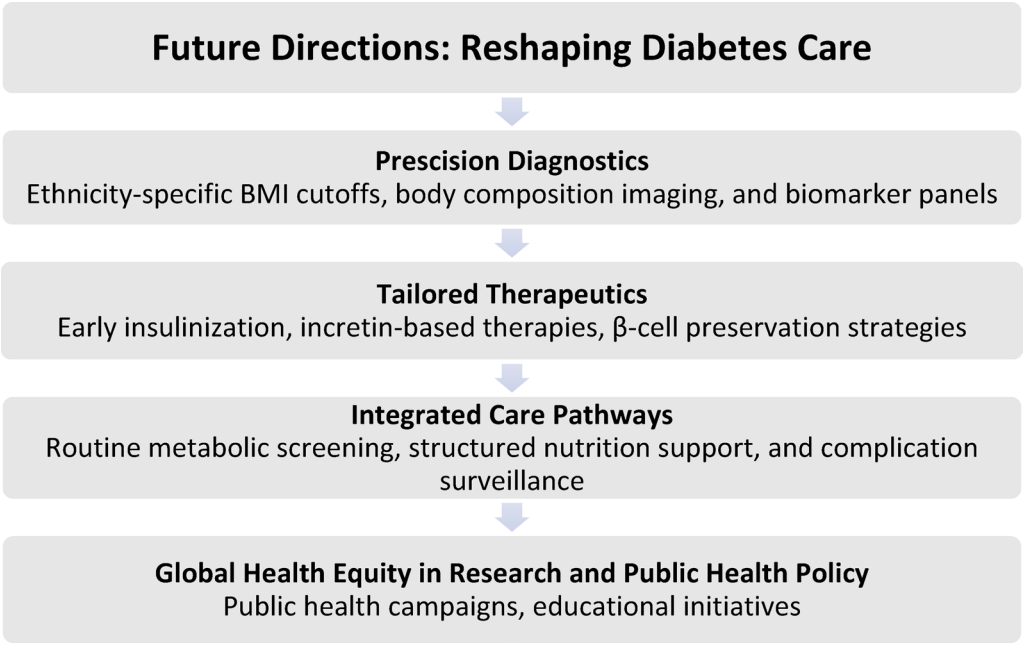

Fig. 2 Proposed Care Pathway for Lean Type 2 Diabetes

1. Heterogeneous terminology across studies ("lean diabetes," "normal weight diabetes," "non-obese T2DM") complicates literature synthesis.
2. Absence of universally standardized diagnostic criteria for lean T2DM.
3. BMI thresholds vary substantially across populations, limiting comparability.
4. Diagnostic overlap with LADA, ketosis-prone diabetes, and MODY creates classification ambiguity.
5. Sparse epidemiological data, particularly from low- and middle-income countries.
6. Virtual absence of randomized controlled trials specifically enrolling lean T2DM patients.
7. Incomplete pathophysiological understanding, with most research focused on overweight populations.
8. Implementation barriers and health system capacity requirements inadequately addressed.
9. Proposed clinical approaches represent expert consensus derived from observational investigations rather than guideline-endorsed recommendations from international diabetes organizations (ADA, EASD, IDF, WHO), which maintain BMI-independent treatment frameworks pending randomized trial evidence in lean cohorts.
10. Mechanistic measurements (C-peptide, HOMA indices, insulin sensitivity) lacking across most lean T2DM literature.
11. Body composition assessed by crude surrogates (BMI, waist circumference) rather than direct measurement (imaging, body fat percentage).

Conclusions

Lean type 2 diabetes represents an under-recognized phenotype with documented population-specific patterns, though evidence limitations explain why major diabetes organizations maintain unified protocols. The absence of randomized controlled trials in lean patients constrains guideline development despite observational data supporting ethnic-adjusted screening thresholds [111–113].

Proposed management strategies emphasizing β-cell preservation reflect expert consensus requiring validation through dedicated trials, health economic analyses, and implementation research. Fundamental questions remain unresolved: whether lean T2DM constitutes a distinct pathophysiological entity and whether treatment responses justify stratified algorithms.

Lean T2DM shows population-specific patterns, but mechanistic evidence remains limited. The critical gap is absence of standardized measurement of β-cell function and insulin sensitivity across BMI-stratified cohorts. Current recommendations infer mechanisms from outcomes without direct validation. Proposed treatments (e.g., early GLP-1 for presumed β-cell failure) require prospective studies incorporating: Standardized C-peptide/HOMA assessment, documented insulin sensitivity measurement and body composition quantification (visceral imaging, hepatic lipid) [44].

This mechanistic characterization not BMI categorization alone should guide guideline development and treatment algorithms. Implementation depends on establishing consensus measurement thresholds and validating

that treatment responses actually differ by mechanistic phenotype.

Acknowledgements
The author thanks the librarian of Maulana Azad Medical College for literature search support.

Author contributions
Author conceived the review concept, designed the search methodology, conducted comprehensive literature searches, performed data extraction and analysis, and drafted the complete manuscript including tables and figures.

Funding
No specific funding was received for this work.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
This review article does not involve human or animal subjects.

Competing interests
The authors declare no competing interests.

AI assistance declaration
This work utilized AI (Claude 4) assistance for language enhancement and editing. The author reviewed all content and accepts full responsibility for the manuscript.

Clinical trial registration number
Not applicable.

Received: 3 September 2025 / Accepted: 27 October 2025
Published online: 26 November 2025

References

1. Yajnik CS. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. J Nutr. 2004;134(1):205–10. https://doi.org/10.1093/jn/134.1.205.
2. Ma RCW, Chan JCN. Type 2 diabetes in East asians: similarities and differences with populations in Europe and the united States. Ann N Y Acad Sci. 2013;1281:64–91. https://doi.org/10.1111/nyas.12098.
3. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018;6(5):361–9. https://doi.org/10.1016/S2213-8587(18)30051-2.
4. Prasad RB, Groop L. Genetics of type 2 diabetes–pitfalls and possibilities. Genes. 2015;6(1):87–123. https://doi.org/10.3390/genes6010087.
5. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs white Caucasians. Int J Obes. 2011;35(2):167–87. https://doi.org/10.1038/ijo.2010.135.
6. Mbanya JC, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. Lancet. 2010;375(9733):2254–66. https://doi.org/10.1016/S0140-6736(10)60550-8.
7. Hennis A, Wu SY, Nemesure B, Li X, Leske MC. Diabetes in a Caribbean population: epidemiological profile and implications. Int J Epidemiol. 2002;31(1):234–9. https://doi.org/10.1093/ije/31.1.234.
8. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–63. https://doi.org/10.1016/S0140-6736(03)15268-3.
9. Caleyachetty R, Thomopoulos C, Tait CA, et al. Ethnicity-specific BMI thresholds for screening and intervention in minority populations: a population-based cohort study in England. Lancet Diabetes Endocrinol. 2021;9(7):419–26. https://doi.org/10.1016/S2213-8587(21)00088-7.
10. Teufel F, Seiglie JA, Geldsetzer P, Theilmann M, Marcus ME, Ebert C, et al. Body-mass index and diabetes risk in 57 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 685 616 adults. Lancet. 2021;398(10296):238–48. https://doi.org/10.1016/S0140-6736(21)00844-8.
11. American Diabetes Association Professional Practice Committee. Standards of care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1):S1–321. https://doi.org/10.2337/dc25-Sint.
12. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the ADA and the EASD. Diabetes Care. 2022;45(11):2753–86. https://doi.org/10.2337/dci22-0034.
13. Nishimura R, Kanda A, Sano H, Matsudaira T, Morimoto A, Tajima N. Glycemic control and medication use in lean vs. obese Japanese patients with type 2 diabetes. J Diabetes Investig. 2019;10(5):1225–33. https://doi.org/10.1111/jdi.13017.
14. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA. 2009;301(20):2129–40. https://doi.org/10.1001/jama.2009.726.
15. Katzmarzyk PT, Bray GA. Ethnic differences in the relation between obesity and diabetes risk. Obes Rev. 2003;4(3):133–8. https://doi.org/10.1046/j.1467-789X.2003.00105.x.
16. Rush EC, Plank LD, Laulu MS, Robinson SM, Parnell WR, Beaglehole R. Body size, body composition, and fat distribution: a comparison of Pacific Islands and new Zealand Europeans. Int J Obes Relat Metab Disord. 1997;21(12):1124–31. https://doi.org/10.1038/sj.ijo.0800522.
17. Ramachandran A, Snehalatha C, Vijay V. Low risk threshold for acquired diabetogenic factors in Asian Indians. Diabetes Res Clin Pract. 2004;65(3):189–95. https://doi.org/10.1016/j.diabres.2004.01.014.
18. Mohan V, Deepa R, Deepa M, Somannavar S, Datta M. A simplified Indian diabetes risk score for screening for undiagnosed diabetic subjects. J Assoc Physicians India. 2005;53:759–63.
19. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368(9548):1681–8. https://doi.org/10.1016/S0140-6736(06)69703-1.
20. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. Prevalence of diabetes and prediabetes in urban and rural india: phase I results of the ICMR–INDIAB study. Diabetologia. 2011;54(12):3022–7. https://doi.org/10.1007/s00125-011-2291-5.
21. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF. Diabetes in Africans. Part 2: Ketosis-prone atypical diabetes mellitus. Diabetes Metab. 2002;28(1):5–12.
22. Balti EV, Kengne AP, Sobngwi E, et al. Ketosis-prone type 2 diabetes in sub-Saharan africans: clinical and metabolic characteristics. Diabetes Metab Res Rev. 2015;31:713–21. https://doi.org/10.1002/dmrr.2652.
23. Hennis AJ, Wu SY, Nemesure B, Leske MC, Barbados Eye Studies Group. Diabetes in a Caribbean population: prevalence and associated risk factors. Diabetes Care. 2002;25(10):1648–53. https://doi.org/10.2337/diacare.25.10.1648.
24. Ferguson TS, Tulloch-Reid MK, Wilks RJ. The epidemiology of diabetes mellitus in Jamaica and the Caribbean: a historical review. West Indian Med J. 2010;59(3):259–64.
25. Gulliford MC, Mahabir D. Diabetes in trinidad: prevalence and associated factors. Diabet Med. 1999;16(10):875–80. https://doi.org/10.1046/j.1464-5491.1999.00143.x.
26. Unwin N, Alberti KG, Bennett N, McLarty D, Tuomilehto J, Wilks R. Diabetes in the caribbean: results of a population survey from Jamaica. Diabet Med. 1999;16(10):875–80. https://doi.org/10.1046/j.1464-5491.1999.00143.x.
27. Looker HC, Knowler WC, Hanson RL. Changes in BMI and weight before and after the development of type 2 diabetes. Diabetes Care. 2001;24(11):1917–22. https://doi.org/10.2337/diacare.24.11.1917.
28. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med. 1995;122(7):481–6. https://doi.org/10.7326/0003-4819-122-7-199504010-00001.
29. UK Prospective Diabetes Study (UKPDS) Group. Characteristics of newly presenting type 2 diabetic patients: analysis of 4,031 patients in the UKPDS. Diabet Med. 1990;7(9):706–12. https://doi.org/10.1111/j.1464-5491.1990.tb01473.x.
30. Grant SF, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38(3):320–3. https://doi.org/10.1038/ng1732.
31. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet. 2010;375(9712):408–18. https://doi.org/10.1016/S0140-6736(09)60937-5.

32. Hodge AM, Dowse GK, Collins VR, Zimmet PZ. Abnormal glucose tolerance and diabetes in the Pacific: relation to body mass index and obesity. Int J Obes Relat Metab Disord. 1996;20(9):795–800.
33. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol. 2014;2(1):56–64. https://doi.org/10.1016/S2213-8587(13)70112-8.
34. Balcha SA, Phillips DIW. Insulin requirement in ketosis-prone diabetes: a systematic review and meta-analysis. Diabet Med. 2021;38(3):e14459. https://doi.org/10.1111/dme.14459.
35. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. Endocr Rev. 2008;29(3):292–302. https://doi.org/10.1210/er.2007-0026.
36. Hennis AJM, Fraser HS, White S, et al. Prevalence of diabetes among Afro-Caribbean adults: results from a population-based survey in Barbados. Diabetes Care. 2002;25(7):1191–6. https://doi.org/10.2337/diacare.25.7.1191.
37. Wilks RJ, Rotimi CN, Bennett FI, McFarlane-Anderson N, Kaufman JS, Anderson SG, et al. Diabetes in the caribbean: results of a population survey from Spanish Town, Jamaica. Diabet Med. 1999;16(10):875–83. https://doi.org/10.1046/j.1464-5491.1999.00143.x.
38. Gulliford MC, Mahabir D, Rocke B. Diabetes-related morbidity in a Caribbean island: the St James Survey, Trinidad. J Epidemiol Community Health. 1996;50(2):123–8. https://doi.org/10.1136/jech.50.2.123.
39. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53. https://doi.org/10.1016/S0140-6736(98)07019-6.
40. Carlsson S. Latent autoimmune diabetes in adults (LADA): A hybrid form of diabetes. Front Physiol. 2019;10:320. https://doi.org/10.3389/fphys.2019.00320.
41. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care. 2009;32(2):287–94. https://doi.org/10.2337/dc08-1296.
42. George AM, Jacob AG, Fogelfeld L. Lean diabetes mellitus: an emerging entity in the era of obesity. World J Diabetes. 2015;6(4):613–20. https://doi.org/10.4239/wjd.v6.i4.613.
43. Hosokawa Y, Kozawa J, Nishizawa H, Kawamori D, Maeda N, Otsuki M, Matsuoka TA, Iwahashi H, Shimomura I. Positive correlation between fasting plasma glucagon and serum C-peptide in Japanese patients with diabetes. Heliyon. 2019;5(5):e01715. PMID: 31193194; PMCID: PMC6520599.
44. Salvatore T, Galiero R, Caturano A, Rinaldi L, Criscuolo L, Di Martino A, et al. Current knowledge on the pathophysiology of lean/normal-weight type 2 diabetes. Int J Mol Sci. 2022;24(1):658. https://doi.org/10.3390/ijms24010658.
45. Consultation on Nutritional Guidelines for the Management of Asian Populations. BMI cut-offs to define overweight and obesity in Asians differ from those in Europeans. Diabetes Res Clin Pract. 2019;155:107819. https://doi.org/10.1016/j.diabres.2019.107819.
46. Kodama K, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, Yachi Y, et al. Ethnic differences in the relationship between BMI and diabetes incidence: a meta-analysis. Diabetes Care. 2012;35(6):1753–60. https://doi.org/10.2337/dc11-1843.
47. Swinburn BA, Ley SJ, Carmichael HE, Plank LD. Body size and composition in Polynesians. Int J Obes. 1999;23(11):1178–83. https://doi.org/10.1038/sj.ijo.0801053.
48. International Diabetes Federation. IDF Diabetes Atlas, 10th edition. Brussels: International Diabetes Federation; 2023.
49. Després JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012;126(10):1301–13. https://doi.org/10.1161/CIRCULATIONAHA.111.067264.
50. Lear SA, Humphries KH, Kohli S, Birmingham CL. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. Obesity. 2007;15(11):2817–24. https://doi.org/10.1038/oby.2007.334.
51. Ruderman NB, Schneider SH, Berchtold P. The metabolically-obese, normal-weight individual. Am J Clin Nutr. 1981;34(8):1617–21. https://doi.org/10.1093/ajcn/34.8.1617.
52. Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab. 2017;26(2):292–300. https://doi.org/10.1016/j.cmet.2017.07.008.
53. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. Lancet Diabetes Endocrinol. 2025;13(2):134–48. https://doi.org/10.1016/S2213-8587(24)00338-7.
54. Stefan N, Schick F, Birkenfeld AL, Häring HU, White MF. The role of hepatokines in NAFLD. Cell Metab. 2023;35(2):236–52. https://doi.org/10.1016/j.cmet.2023.01.006.
55. Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, Twombly JG, et al. Glucose-independent, black-white differences in hemoglobin A1c levels. Ann Intern Med. 2010;152(12):770–7. https://doi.org/10.7326/0003-4819-152-12-201006150-00004.
56. Nakagami T. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. Diabetologia. 2004;47(3):385–94. https://doi.org/10.1007/s00125-004-1334-6.
57. Vassy JL, Meigs JB. Is genetic testing useful to predict type 2 diabetes? Best Pract Res Clin Endocrinol Metab. 2012;26(2):189–201. https://doi.org/10.1016/j.beem.2011.09.004.
58. Kavakiotis I, Tsave O, Salifoglou A, Maglaveras N, Vlahavas I, Chouvarda I. Machine learning and data mining methods in diabetes research. Comput Struct Biotechnol J. 2017;15:104–16. https://doi.org/10.1016/j.csbj.2016.12.005.
59. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013;30(7):803–17. https://doi.org/10.1111/dme.12159.
60. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487–95. https://doi.org/10.2337/diacare.27.6.1487.
61. Pfützner A, Forst T. Elevated intact proinsulin levels are indicative of Beta-cell dysfunction, insulin resistance, and cardiovascular risk: impact of the anti-diabetic agent Pioglitazone. J Diabetes Sci Technol. 2011;5(3):784–93. PMID: 21722594; PMCID: PMC3192645.
62. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–95. https://doi.org/10.2337/db09-9028.
63. Jaiswal A, Vijayaraghavan R, Nair S. The pathophysiology of type 2 diabetes mellitus in non-obese individuals: an overview of the current Understanding. Cureus. 2019;11(10):e6171. https://doi.org/10.7759/cureus.6171.
64. Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, Wei J, Narayan KMV, Ali MK. Long-term sustainability of diabetes prevention approaches: A systematic review and Meta-analysis of randomized clinical trials. JAMA Intern Med. 2017;177(12):1808–17. PMID: 29114778; PMCID: PMC5820728.
65. Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. BMJ Open. 2015;5(8):e008222. https://doi.org/10.1136/bmjopen-2015-008222.
66. Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, et al. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. JAMA. 2008;300(23):2742–53. https://doi.org/10.1001/jama.2008.808.
67. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab. 2014;20(6):953–66. https://doi.org/10.1016/j.cmet.2014.09.018.
68. Leighton E, Sainsbury CA, Jones GC. A practical review of C-peptide testing in diabetes. Diabetes Ther. 2017;8(3):475–87. https://doi.org/10.1007/s13300-017-0265-4.
69. Wang X, Wu N, Sun C, Jin D, Lu H. Effects of SGLT-2 inhibitors on adipose tissue distribution in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2023;15(1):113. https://doi.org/10.1186/s13098-023-01085-y.
70. Fourlanos S, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, et al. Latent autoimmune diabetes in adults (LADA) should be less latent. Diabetologia. 2005;48(11):2206–12. https://doi.org/10.1007/s00125-005-1960-7.
71. Remedios L, Cho C, Schwartz T, Su D, Rudravaram G, Gao C, et al. Data-Driven abdominal phenotypes of type 2 diabetes in Lean, Overweight, and obese cohorts. ArXiv Preprint. 2025. https://doi.org/10.48550/arXiv.2508.11063.
72. Prasad RB, Groop L. Precision medicine in type 2 diabetes. J Intern Med. 2019;285(1):40–8. https://doi.org/10.1111/joim.12859.
73. Chung WK, Erion K, Florez JC, et al. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(7):1617–35. https://doi.org/10.2337/dci20-0022.
74. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. JAMA. 2012;308(6):581–90. https://doi.org/10.1001/jama.2012.9282.

75. Tobias DK, Pan A, Jackson CL, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med. 2014;370(3):233–44. https://doi.org/10.1056/NEJMoa1304501.
76. Saisho Y. Importance of Beta Cell Function for the Treatment of Type 2 Diabetes. J Clin Med. 2014;3(3):923–43. https://doi.org/10.3390/jcm3030923.
77. George AM, Jacob AG, Fogelfeld L. Lean diabetes mellitus: an emerging entity in the era of obesity. World J Diabetes. 2015;6(4):613–25. https://doi.org/10.4239/wjd.v6.i4.613.
78. Nishimura R, Kanda A, Sano H, et al. Glycemic control and insulin therapy in lean versus obese patients with type 2 diabetes: a 10-year cohort study. Diabetes Res Clin Pract. 2019;148:180–7. https://doi.org/10.1016/j.diabres.2019.01.004.
79. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22. https://doi.org/10.1056/NEJMoa1603827.
80. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57. https://doi.org/10.1056/NEJMoa1611925.
81. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57. https://doi.org/10.1056/NEJMoa1812389.
82. Kim NH, Lee J, Kim TJ, et al. Body mass index and mortality in Asian patients with type 2 diabetes: pooled analysis of 18 prospective cohorts. Diabetes Care. 2015;38(11):1967–76. https://doi.org/10.2337/dc15-0760.
83. Mohan V, Pradeepa R. Epidemiology of diabetes in different regions of India. Health Administrator. 2009;22(1–2):1–18.
84. Huang ES, Jr H-YL, Liu J, Jin S, Brown CLH, Meltzer DO, et al. Resource use associated with type 2 diabetes in Africa, the middle East, South Asia, Eurasia and turkey: results from the international diabetes management practice study (IDMPS). Diabetologia. 2016;59(1):234–42. https://doi.org/10.1007/s00125-015-3754-6.
85. Fourlanos S, Perry C, Stein MS, et al. A clinical screening tool identifies autoimmune diabetes in adults. Diabetes Care. 2006;29(5):970–5. https://doi.org/10.2337/diacare.29.05.06.dc05-2101.
86. Liu J, Bai R, Chai Z, Cooper ME, Zimmet PZ, Zhang L. Low- and middle-income countries demonstrate rapid growth of type 2 diabetes: an analysis based on global burden of disease 1990–2019 data. Diabetologia. 2022;65(8):1339–52. https://doi.org/10.1007/s00125-022-05669-6.
87. Screening for Prediabetes and Diabetes. Clinical performance and implications for health equity. J Gen Intern Med. 2023;38(11):2973–80. https://doi.org/10.1007/s11606-023-08299-4.
88. Chiu M, Austin PC, Manuel DG, et al. Deriving ethnic-specific BMI cutoffs for assessing diabetes risk. Diabetes Care. 2011;34(8):1741–8. https://doi.org/10.2337/dc10-2300.
89. Chan JCN, Lim LL, Wareham NJ, Shaw JE, Orchard TJ, Zhang P, et al. The lancet commission on diabetes: using data to transform diabetes care and patient lives. Lancet. 2021;396(10267):2019–82. https://doi.org/10.1016/S0140-6736(20)32374-6.
90. Stefan N, Schulze MB. Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment. Lancet Diabetes Endocrinol. 2023;11(6):426–40. https://doi.org/10.1016/S2213-8587(23)00086-4.
91. Early-onset. Type 2 diabetes mellitus: an update. Endocrine. 2024;67(3):505–15. https://doi.org/10.1007/s12020-024-04027-5.
92. O'Neal KS, Johnson JL, Panak RL. Recognizing and appropriately treating latent autoimmune diabetes in adults. Diabetes Spectr. 2016;29(4):249–52. https://doi.org/10.2337/ds15-0047.
93. Hope SV, Knight BA, Shields BM, McDonald TJ, Hattersley AT, Jones AG. Random non-fasting C-peptide: bringing robust assessment of endogenous insulin secretion to the clinic. Diabet Med. 2016;33(11):1554–8. https://doi.org/10.1111/dme.13142.
94. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia. 2019;62(1):3–16. https://doi.org/10.1007/s00125-018-4711-2.
95. Chaudhary P, Laloo D, Salam R. Prevalence of lean type 2 diabetes mellitus in recently diagnosed type 2 diabetes mellitus patients. Indian J Endocrinol Metab. 2013;17(Suppl1):S316–7. https://doi.org/10.4103/2230-8210.119608.
96. Skinner J, et al. Improving the prevention and treatment of lean type 2 diabetes in sub-Saharan africa: A review. Ethiop J Sci Dev Res. 2025;1(1):1–10.
97. Taylor R. Type 2 diabetes: etiology and reversibility. Diabetes Care. 2013;36:1047–55. https://doi.org/10.2337/dc12-1805.
98. Salvatore T, Galiero R, Masullo M, Macchia PE, Morisco C, Sardu C, et al. Lean type 2 diabetes: pathophysiology, clinical features, and management. Int J Mol Sci. 2023;24(1):658. https://doi.org/10.3390/ijms24010658.
99. Misra A, Shrivastava U. Obesity and dyslipidemia in South Asians. Nutrients. 2013;5(7):2708–33. https://doi.org/10.3390/nu5072708.
100. Lear SA, Humphries KH, Kohli S, Birmingham CL. Ethnic-specific criteria for classification of body mass index: A perspective on South Asians. Int J Obes (Lond). 2009;33:781–6. https://doi.org/10.1038/ijo.2009.68.
101. Kim KS, Kim SK, Lee YK, et al. Mortality and cardiovascular risk in lean and obese type 2 diabetes: a nationwide cohort study. J Clin Endocrinol Metab. 2015;100(11):4237–45. https://doi.org/10.1210/jc.2015-2553.
102. Lim S, Kim KM, Choi SH, Kang SM, Park YJ, Jang HC, et al. Increasing prevalence of lean type 2 diabetes in Korean adults: a population-based study. BMC Public Health. 2024;24:1034. https://doi.org/10.1186/s12889-024-18509-y.
103. Sharma M, John R, Afrin S, Zhang X, Wang T, Tian M, et al. Cost-effectiveness of population screening programs for cardiovascular diseases and diabetes in low- and middle-income countries: a systematic review. Front Public Health. 2022;10:820750. https://doi.org/10.3389/fpubh.2022.820750.
104. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152–62. https://doi.org/10.1016/S2213-8587(13)70062-7.
105. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44–56. https://doi.org/10.1038/s41591-018-0300-7.
106. Viswanathan Mohan TA, Pramodkumar M, Deepa R, Pradeepa R, Unnikrishnan P, Routray, et al. Lean diabetes is one end of the spectrum of type 2 diabetes and not a separate entity. Diabetes Res Clin Pract. 2025;227:112387. https://doi.org/10.1016/j.diabres.2025.112387.
107. Chung W, Choi Y, Lee S, et al. Insulin resistance and β-cell function of lean versus overweight/obese newly diagnosed type 2 diabetes mellitus patients. Diabetes Metab J. 2020;44(5):617–25. https://doi.org/10.4093/dmj.2019.0129.
108. AGORA Diabetes Collaborative Group. Diabetes syndrome-based staging and phenotype-specific care pathways: a practical proposal. Diabetologia. 2023;66(9):1552–62. https://doi.org/10.1007/s00125-023-05947-5.
109. Kengne AP, Ramachandran A. Feasibility of prevention of type 2 diabetes in low- and middle-income countries. Diabetologia. 2024;67(5):763–72. https://doi.org/10.1007/s00125-024-06091-8.
110. Puhl R, Himmelstein MS, Speight J. Weight stigma and diabetes stigma: implications for weight-related health behaviors in adults with type 2 diabetes. Clin Diabetes. 2022;40(1):51–61. https://doi.org/10.2337/cd21-0084.
111. Yamamoto JF, Goodman PJ. Epidemiology of type 2 diabetes in Caribbean and Pacific Islander populations: genetic predisposition and environmental influences. Diabetes Res Clin Pract. 2024;197:110858. https://doi.org/10.1016/j.diabres.2024.110858.
112. Papua M, et al. Prevalence of diabetes and prediabetes in South Asian countries: a systematic review and meta-analysis. Discover Public Health. 2025;22:39. https://doi.org/10.1186/s44258-025-00039-5.
113. Nolan CJ, Peyrot M, Zehle MR, et al. Interventions to address global inequity in diabetes: international progress. Lancet Diabetes Endocrinol. 2023;11:842–56. https://doi.org/10.1016/S2213-8587(23)00264-9.

Publisher's note