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LEAN NON-AUTOIMMUNE DIABETES IN ADULTS IN THE TROPICS

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ABSTRACT

Lean non-autoimmune diabetes represents a heterogeneous group of disorders characterized by hyperglycemia in individuals with normal or low body mass index (BMI), in the absence of autoimmune beta-cell destruction. Defining the condition is challenging due to inconsistent terminology and the variability in BMI cut-offs. Pathophysiologically, it is driven by beta-cell dysfunction influenced by genetic predisposition, fetal undernutrition with epigenetic programming, and chronic glucotoxic and lipotoxic stress. Although insulin resistance is usually milder, visceral and ectopic adiposity and sarcopenia play a defining role in the pathogenesis. Major subtypes include malnutrition-related diabetes mellitus (MRDM), fibrocalcific pancreatic diabetes (FCPD), ketosis-prone diabetes (KPD), and maturity-onset diabetes of the young (MODY). MRDM, now recognized as type 5 diabetes, is linked to chronic undernutrition. It typically affects adolescents and young adults in tropical, low-resource settings and is characterized by very low BMI, reduced beta-cell function, and absence of ketosis. FCPD, another subtype, arises from chronic non-alcoholic calcific pancreatitis and is marked by progressive beta-cell loss and exocrine insufficiency with pancreatic ductal stones and malabsorption. KPD presents with unprovoked or minimally provoked diabetic ketoacidosis in individuals without autoimmune markers, but typically, the beta-cell function recovers, allowing insulin independence. Together, these forms represent the principal categories of lean non-autoimmune diabetes observed in tropical populations. Insulin remains the mainstay of treatment because of primary beta-cell failure. At the same time, care must focus on adequate nutrition, correction of micronutrient deficiencies, and resistance exercise to preserve muscle mass and enhance insulin sensitivity. Future work should integrate genomic, epigenetic, and microbiome insights to refine classification and improve outcomes through precision-based approaches.

INTRODUCTION

Lean non-autoimmune diabetes represents a distinct phenotype characterized by hyperglycemia with normal or low body mass index (BMI) in the absence of autoimmune beta-cell destruction. The term encompasses a broad, heterogeneous group that does not conform to the conventional association between obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). Despite being frequently

encountered, there is no universally accepted definition. Existing literature uses inconsistent terminology, diagnostic criteria, and classification systems, leading to significant variability in how the condition is described and studied.

DEFINITION OF LEAN DIABETES AND KEY CHALLENGES

A key challenge in defining lean diabetes is the lack of standardized BMI cut-offs. The World Health Organization (WHO) classifies underweight as BMI <18.5 kg/m² and normal weight as 18.5–24.9 kg/m² (1). However, such categorization fails to account for ethnic differences in body fat distribution and metabolic risk. Asians, particularly South Asians, tend to develop T2DM at a lower BMI due to greater visceral fat, leading the WHO to recommend an upper normal cut-off of 23 kg/m² for this population (2).

A BMI of 18.5 kg/m² defines the lower limit of the normal range. The distinction between lean and underweight is clinically relevant. Individuals with BMI between 18.5–23 kg/m² may have preserved muscle mass but exhibit insulin resistance due to visceral and ectopic lipid deposition, a pattern often seen in the "thin-fat" phenotype of South Asians (3). Conversely, those with BMI below 18.5 kg/m² may have underlying chronic malnutrition and sarcopenia, with an increased likelihood of fibrocalcific pancreatic diabetes (FCPD) or malnutrition-related diabetes mellitus (MRDM) (4). While both groups fall under the umbrella of lean diabetes, the pathophysiology, prognosis, and treatment differ. Recent efforts to subclassify diabetes using data-driven cluster analyses have shed light on the heterogeneity within lean diabetes (5,6).

From a pathophysiological perspective, lean diabetes may arise from multiple overlapping mechanisms. These include genetically determined beta-cell dysfunction, sarcopenia, ectopic fat deposition, early-life malnutrition, and epigenetic programming due to intrauterine growth restriction (IUGR). The “thrifty phenotype” hypothesis is particularly relevant here, proposing that fetal adaptations to undernutrition result in metabolic inflexibility and impaired beta-cell development (7).

A comprehensive and operational criteria for lean non-autoimmune diabetes should include BMI <23 kg/m² in Asians and <25 kg/m² globally, with a note for underweight (<18.5 kg/m²) as a special sub-phenotype; negative autoimmune markers (GAD65, IA-2, ZnT8, ICA); documented C-peptide levels to rule out absolute insulin deficiency; and consideration of body composition metrics, such as muscle mass and visceral adiposity (8,9). Until such a consensus is reached, lean diabetes remains a “diagnostic umbrella” encompassing a variety of non-obese diabetes phenotypes. Table 1 summarizes the key characteristics of lean diabetes.

Table 1. Characteristic Features of Lean Diabetes	
Feature	**Description**
BMI criteria	<18.5 kg/m² - MRDM or type 5 diabetes <23 kg/m² (Asians) <25 kg/m² (global standard)
Autoantibody status	Negative for GAD65, IA-2, ZnT8, ICA
C-peptide	Low to low-normal; reduced beta-cell reserve
Insulin resistance	Mild to moderate; due to ectopic fat, sarcopenia, or visceral adiposity
Ketosis at onset	Typically absent; may be present in ketosis-prone variants
Muscle mass	Often reduced (sarcopenia), especially in undernourished or elderly
Fat distribution	Visceral or ectopic adiposity despite low BMI ('thin-fat' phenotype)
Age of onset	Frequently <40 years; may occur in <30 years in presence of malnutrition
Nutritional history	Early-life undernutrition, low birth weight, and stunting
Family history	May or may not be present; variable across population
Treatment response	Insulin often needed early, response to insulin secretagogues in some

EPIDEMIOLOGY

Lean or normal-weight individuals from Asia, Africa, and Latin America are at increased risk of developing T2DM compared to Caucasians with a similar BMI (10,11). In countries such as Sweden, the United Kingdom, and Australia, lean individuals constitute approximately 5–15% of the T2DM population and often exhibit distinct demographic and metabolic profiles (12,13). In South and Southeast Asian countries such as India, Bangladesh, Sri Lanka, and Indonesia, over 40% of individuals with diabetes have a BMI <25 kg/m². Studies from India, including the ICMR-INDIAB and CARRS cohorts, have reported that 30–50% of adults with newly diagnosed diabetes are lean or within the normal-weight range (14,15). A meta-analysis of 11 observational studies from Africa reported a 38.5% prevalence of lean T2DM (BMI <25 kg/m²) with a mean age of 48.3 years (16).

PATHOPHYSIOLOGY

Central Role of Beta-Cell Dysfunction

A consistent finding in lean diabetes is marked beta-cell dysfunction (5,6,17,18). Unlike obese T2DM, where insulin resistance is the primary pathology, lean diabetes is marked by early and severe insulin secretory defects, with lower fasting and stimulated insulin and C-peptide levels (19). Studies report reduced homeostatic model assessment of beta-cell function (HOMA-B) scores in lean diabetes (20). In the Chennai Urban Rural Epidemiology Study (CURES), lean individuals with diabetes showed diminished insulinogenic index and disposition index, confirming a primary insulin secretory defect (17).

Cluster analysis studies in Scandinavia and later in India stratified newly diagnosed diabetes into phenotypic subgroups using age, BMI, insulin resistance, autoimmunity, and beta-cell function (5,6). Among Indian cohorts, the severe insulin-deficient diabetes (SIDD) cluster was dominant, especially among lean individuals, accounting for over 40–50% of cases (6). This pattern contrasts with the European population, where the mild obesity-related diabetes (MOD) cluster is more common (5). The beta-cell dysfunction is not always progressive and may reflect a combination of intrinsic and acquired factors. Several hypotheses have been proposed to explain the early failure of beta-cell function in lean diabetes.

GENETIC PREDISPOSITION

Specific populations may have a higher burden of genetic variants linked to beta-cell insufficiency. For example, polymorphisms in TCF7L2, HNF1A, and KCNJ11 are known to impair insulin gene transcription and exocytosis (21).

EPIGENETIC PROGRAMMING

Nutritional deprivation during fetal and early postnatal life can induce persistent changes in beta-cell mass and function. Evidence from animal studies and human cohorts demonstrates a consistent association between low birth weight, early growth failure, and reduced beta-cell function in later life (7,22).

GLUCOTOXICITY AND LIPOTOXICITY

In lean individuals, ectopic fat deposition in the pancreas and chronic hyperglycemia may induce oxidative stress and endoplasmic reticulum dysfunction, hastening beta-cell apoptosis (23).

AUTOIMMUNITY

Some cases of lean diabetes may represent latent autoimmune diabetes in adults (LADA) that have been misclassified. Autoantibody-negative individuals with severe insulin deficiency may exhibit immune-mediated beta-cell injuries not captured by standard markers (24).

Insulin Resistance and Fat Distribution

Insulin resistance is not uncommon in lean diabetes but differs in pattern from that seen in obesity (20). In lean diabetes, insulin resistance often accompanies abnormal fat distribution, with adiposity skewed toward visceral and ectopic depots despite normal BMI (3,25). A characteristic feature in South Asians is the “thin-fat” phenotype, marked by disproportionately higher visceral fat despite normal BMI (3). Dual-energy X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI) studies show that South Asians have greater visceral and hepatic fat than Europeans at comparable BMI (26,27).

The unique fat distribution contributes to metabolic dysfunction. Visceral fat is metabolically active and secretes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and resistin that impair insulin signaling (28). Furthermore, lipolysis in visceral fat depots increases the flux of free fatty acids to the liver, promoting hepatic insulin resistance and gluconeogenesis.

Ectopic fat accumulation in the liver, muscle, and pancreas can further exacerbate insulin resistance. In lean individuals, metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly linked to impaired hepatic insulin extraction and systemic insulin resistance (29). Intramyocellular lipid deposition impairs skeletal muscle glucose uptake (30). Together, these factors suggest that adipose tissue dysfunction rather than total fat mass is a key driver of insulin resistance (31). The degree of insulin resistance is often milder, but due to concurrent beta-cell dysfunction, even modest resistance can precipitate hyperglycemia (19).

Sarcopenia and Muscle-Fat Composition

Sarcopenia is a key determinant of insulin resistance and dysglycemia in lean diabetes, with reduced muscle mass and altered muscle fat composition playing a dominant pathogenic role (32). Skeletal muscle accounts for about 80% of postprandial glucose uptake; thus, reduced muscle mass directly impairs glucose homeostasis (33). Individuals with lower appendicular skeletal muscle mass index (ASMI) exhibit increased insulin resistance, higher fasting glucose levels, and greater risk for progression to diabetes, even after adjusting for BMI and fat mass.

The reduction in muscle mass is often accompanied by an increase in intramuscular and intermuscular fat, which impairs insulin signaling (34). Abnormal muscle fat infiltration, termed myosteatosis, promotes mitochondrial dysfunction and inflammation and reduces insulin receptor phosphorylation (35). MRI and computed tomography (CT) images have

revealed that lean diabetes may be associated with lower muscle attenuation values, an indicator of increased fat content, compared to healthy controls (36).

Nutritional inadequacy, physical inactivity, chronic inflammation, and age-related decline in anabolic hormones such as testosterone, growth hormone, and IGF-1 are major contributors to sarcopenia (37). Early-life undernutrition and stunting may result in persistently low muscle mass during adulthood, predisposing individuals to metabolic dysfunction. The coexistence of sarcopenia and visceral adiposity, termed sarcopenic obesity, creates a unique metabolic milieu that elevates diabetes risk. The phenotype may not be captured by BMI assessment, emphasizing the need for body composition assessment (38,39).

Genetic and Epigenetic Drivers

Genome-wide association studies (GWAS) have identified multiple loci linked to beta-cell function, insulin secretion, and glucose metabolism that are overrepresented in lean diabetes (40). Most consistently implicated genes are variants in TCF7L2, HHEX, CDKN2A/B, KCNJ11, HNF1A, and MTNR1B (41). These genes are predominantly associated with impaired insulin secretion (42). The risk allele frequency of these variants is higher in South Asians, East Asians, and sub-Saharan Africans.

Epigenetics refers to heritable changes in gene expression that occur without altering the DNA sequence, often in response to environmental factors such as nutrition, stress, and toxins. Fetal malnutrition, IUGR, and low birth weight have been linked to increased risk of dysglycemia in adulthood (7,22). The “thrifty phenotype” hypothesis suggests that undernutrition during critical periods of fetal development induces permanent changes in insulin sensitivity and beta-cell mass (7). These changes may confer survival advantages in nutrient-scarce environments but become maladaptive when exposed to calorie excess later (43). Epigenetic modifications such as DNA methylation, histone acetylation, and non-coding RNA expression have been identified in genes regulating pancreatic development, insulin signaling, and energy metabolism (44).

Human epigenome-wide association studies (EWAS) and animal models demonstrate that early-life nutritional insults can program metabolic pathways with transgenerational effects (45). DNA methylation changes in the IGF2, PPARγ, and PDX1 genes have been associated with increased diabetes risk and reduced insulin secretion (46). These insights are particularly relevant for regions like South Asia and sub-Saharan Africa, where high rates of maternal and childhood undernutrition coexist with rapidly changing dietary and lifestyle patterns (47).

Developmental Origins of Health and Disease (DOHaD)

The DOHaD hypothesis proposes that environmental exposures, especially nutrition, during fetal life can permanently program physiological systems (48). In animal models, maternal protein restriction has been associated with reduced beta-cell mass, impaired islet vascularization, and lower expression of critical transcription factors such as PDX1, leading to impaired insulin synthesis and secretion (49). Infants born small-for-gestational age (SGA) exhibit a blunted insulinogenic response and increased hepatic glucose production, predisposing them to diabetes.

Malnutrition additionally affects the developmental trajectory of skeletal muscle, liver, adipose tissue, and the central nervous system, particularly the hypothalamic circuits regulating appetite and energy balance. The “dual-hit” mechanism suggests that fetal undernutrition primes susceptibility, while excess energy exposure later in life acts as the trigger for T2DM (48).

Role of Gut Microbiome

Dysbiosis, or an imbalance in gut microbial communities, has been implicated in the development

of insulin resistance and beta-cell dysfunction. Lean diabetes may be associated with unique microbiota changes distinct from dysbiosis in obesity (50). The gut microbiota ferments dietary fiber into short-chain fatty acids (SCFAs) - acetate, propionate, and butyrate - which regulate gut integrity, inflammation, and insulin sensitivity (51). Lean diabetes is associated with reduced microbial diversity and lower levels of SCFA-producing bacteria, such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, that predispose to systemic inflammation and impaired insulin signaling (52).

Dysbiosis disrupts intestinal tight junctions, allowing the translocation of endotoxins. The metabolic endotoxemia induces low-grade inflammation and insulin resistance (53). Gut bacteria also modulate bile acid synthesis and signaling through farnesoid X receptor (FXR) and TGR5. Dysregulated bile acid metabolism may affect lipid absorption, glucose homeostasis, and GLP-1 secretion (54). The gut microbiome additionally regulates immune system maturation and tolerance. Imbalances may activate pro-inflammatory pathways (e.g., IL-1β, TNF-α), contributing to beta-cell stress and dysfunction (55). Early-life environmental exposures, including birth mode, breastfeeding duration, antibiotic use, and dietary diversity, affect the composition of the gut microbiota and may influence the long-term risk of metabolic diseases. In tropical countries where infections and undernutrition are common, early disturbances in microbial colonization may increase the future risk of diabetes.

SUBTYPES OF LEAN DIABETES

Malnutrition–Related Diabetes Mellitus (MRDM) or Type 5 Diabetes

HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY

Initially termed J-type diabetes, MRDM was first described in 1955 by Hugh Jones from Jamaica (56). Subsequently, the condition was reported in several areas of Africa and Asia. In 1965, extensive observations on this variant of diabetes were reported from India (57). This condition has been described under various names, including ketosis-resistant diabetes of the young (KRDY), malnutrition or M type, tropical diabetes, insulin-requiring diabetes mellitus (IRDM), protein-deficient diabetes mellitus (PDDM), and protein-deficient pancreatic diabetes (PDPD). In 1995, an international forum renamed it as MRDM.

Earlier reports indicated that MRDM accounted for 10–25% of childhood- or juvenile-onset diabetes in tropical countries, but its prevalence has declined in recent decades with improved nutrition. Most cases are from rural, low socio-economic backgrounds that consume large carbohydrate meals once or twice daily. Male predominance is noted in India (2.5:1), although sex distribution is similar in Africa. A positive family history is uncommon (<10%), suggesting stronger environmental than genetic influences. However, HLA linkage disequilibrium has been observed in MRDM, with associations to the DR3, DQ2, and DQ9 loci, indicating a genetic background distinct from type 1 diabetes mellitus (T1DM) (58).

PATHOGENESIS OF MRDM

Chronic malnutrition can impair beta-cell function, with recurrent insults leading to overt diabetes, particularly in genetically predisposed individuals (59). Additional mechanisms include increased beta-cell vulnerability to immune attack, environmental toxins, and dietary factors. Prior malnutrition results in a decline in insulin levels in the fasting state and also following a glucose load (60). Additionally, subclinical malnutrition may first cause hyperinsulinemia, which can progress to hypoinsulinemia with chronic undernutrition (61). Animal studies demonstrate that undernutrition leads to reduced beta-cell size and degranulation, and to islets with lower beta-cell concentration and asymmetric staining for insulin (62). Human histological studies show islet hypertrophy in early kwashiorkor, followed by a marked reduction in islet number in later stages (63).

Pyridoxine deficiency impairs insulin secretion in rats, though its specific role in human MRDM remains unclear. Chromium and magnesium have been evaluated for their role in glucose intolerance, acting through tyrosine kinase–mediated insulin signaling, but the evidence remains inconclusive. Vitamin D, through its effects on the inflammatory milieu, may affect insulin secretion. Biotin has been hypothesized to enhance hepatic glucose uptake through hexokinase gene expression (64). However, larger studies are needed to define the role of micronutrient deficiency in MRDM.

Studies from India suggest a possible autoimmune component, with reported antibody positivity rates of about 30% for tyrosine phosphatase, 30% for GAD65, 20% for celiac-specific transglutaminase, and 14% for IA2. In many cases, more than one autoantibody is present (65).
DR7-DQ9 and MICA allele-9 are found to be augmented in autoantibody-negative MRDM.

Studies on sarcopenia and glucose imbalance indicate a vicious cycle in which the accumulation of advanced glycation end-products and reactive oxygen species promote muscle apoptosis. Impaired muscle protein regeneration, further influenced by chromosomal alterations in pathways involving histone deacetylation, Akt/PKB, FoxOs, PGC-1α, and AMPK, contributes to the development of insulin resistance and hyperglycemia (66). Recent work highlights the role of adipose tissue hormones in MRDM. Low-grade adipose tissue inflammation activates IL-1β, TNF-α, and IL-6, promoting β-cell injury via the monocyte–macrophage system. Elevated resistin, leptin, and visfatin, along with reduced adiponectin in low-birth-weight infants, further support the contribution of adipocytokines to the metabolic disturbances characteristic of MRDM (65).

CLINICAL AND BIOCHEMICAL FEATURES

The onset is usually between 10 and 30 years, though isolated cases have been reported in the pre-school years and in those above 30 years of age. Onset is generally marked by osmotic symptoms, with clinical features developing rapidly, although complications may take longer to appear. Family history has been reported variably between 10-20% of subjects (65). Individuals are usually lean, emaciated, with severe weight loss and extreme fatiguability. The BMI is between 11-18 $kg/m^{2,}$ with markers of malnutrition such as skin and hair changes, xerosis, and angular stomatitis being evident in 10–25% of cases.

Microvascular complications such as peripheral neuropathy occur in 10% at the time of presentation. Various pyogenic and fungal skin infections are common, while chronic malnutrition increases susceptibility to pulmonary tuberculosis, which should be excluded in all cases. Premature cataract and diabetic retinopathy are noted in 10–15%. Nephropathy is less common, while macrovascular complications, including coronary artery disease, occur in less than one percent at diagnosis as well as in long-term follow-up. Diabetic ketoacidosis (DKA) is not reported in MRDM. Lack of pancreatic calculi on abdominal imaging distinguishes these subjects from those with FCPD.

Biochemical features include hyperglycemia (usually >250 mg/dl) with a modest rise in cholesterol and triglyceride levels. A striking aspect is the absence of ketosis or ketonuria, with ketosis resistance being attributed to delayed mobilization of free fatty acids from adipose tissue and suppressed postprandial glucagon. Plasma carnitine levels are often reduced in undernourished individuals, and this deficiency impairs free fatty acid transport, a key requirement for beta-oxidation and ketogenesis. Clinical studies have shown ketosis resistance in over 90% of malnourished young individuals with diabetes, further supporting this (67).

INSULIN SECRETION AND INSULIN SENSITIVITY IN MRDM

Fasting insulin and C-peptide levels are usually low or low-normal with minimal response to a normal glucose load (61). Basal and peak insulin and C-peptide are

substantially higher than in T1DM. Studies have documented a minimal rise in insulin levels in response to intravenous tolbutamide (64). High basal growth hormone levels and non-suppressibility following glucose administration are distinctive features reminiscent of protein-energy malnutrition. The basal level of glucagon is raised, but, unlike T1DM, it does not rise further on glucose administration (86).

The relationship between chronic malnutrition and insulin resistance has been studied mainly through surrogate indices. In an euglycemic-hyperinsulinemic clamp study, low-birth-weight Asian Indian males showed subtle features of metabolic syndrome and altered body composition. Clinically, high insulin requirements (>2 U/kg/day) in MRDM suggest possible insulin resistance, though advanced dynamic tests remain limited (68). In an unpublished study on lean (BMI <18 kg/m²) Asian Indian males conducted by one of the authors, the use of isotope-tagged pancreatic clamps, mixed-meal tests, and NMR spectroscopy revealed markedly reduced insulin secretion, heterogeneous hepatic and peripheral insulin resistance, and unexpectedly high visceral and pancreatic adiposity despite low hepatic and muscle fat. These results underscore the complex interplay between beta-cell function, adipose tissue inflammation, and insulin sensitivity and require further characterization.

TREATMENT

Insulin is the mainstay of glycemic control. MRDM may be managed as classic T1DM with additional consideration for nutritional needs. However, the optimal insulin regimens specifically for MRDM have not been studied. Medical nutrition therapy with the right balance of macro- and micronutrients is crucial.

REVIVAL AS TYPE 5 DIABETES

At the recent International Diabetes Federation (IDF) World Diabetes Congress 2025 in Bangkok, Thailand, lean diabetes related to malnutrition was formally classified as “type 5” diabetes, and a working group was established to establish a global research registry and develop education modules to train healthcare professionals in this aspect. However, controversies persist regarding premature categorization without consensus. The distinct clinical features of type 5 diabetes include (69):

•A persistently low BMI < 18.5 kg/m^2 in the background of undernutrition
•Diagnosed with DM before 30 years of age
•No history of DKA in the past
•Predominantly rural origin or living in an area with low socioeconomic status
•Evidence of early life undernutrition: maternal malnutrition, low birth weight, wasting or stunting in childhood, and birth weight < 10th centile for the region of origin

Fibrocalcific Pancreatic Diabetes (FCPD)

INTRODUCTION

FCPD, a form of chronic non-alcoholic calcific pancreatitis, is characterized by pancreatic ductal calculi, exocrine pancreatic insufficiency, and progressive beta-cell dysfunction. It is prevalent in tropical developing countries and is considered a prototype of "tropical pancreatitis". The reader is referred to the chapter entitled “Fibrocalcific pancreatic ” in the Tropical Endocrinology section of Endotext for additional information (4). Table 2 summarizes the clinical features, investigations, and treatment of FCPD.

EPIDEMIOLOGY

FCPD primarily affects young individuals, often presenting in the second or third decade. It is more common in males and is associated with low socioeconomic status and malnutrition. The prevalence in southern parts of India is estimated at about 0.36% among individuals with diabetes and 0.019% in the general population. Recent studies

indicate a declining incidence, likely due to improved nutrition and healthcare.

PATHOGENESIS

The pathogenesis of FCPD is multifactorial. Progressive pancreatic destruction leads to insulin deficiency, but recent research highlights additional roles for insulin resistance and altered body composition. Paradoxical hyperglucagonemia has been observed, possibly originating from extra-pancreatic sources such as intestinal L-cells. Abnormal incretin response, including elevated GLP-1 and oxyntomodulin and reduced GIP, has been documented (70).

Table 2. Clinical Features, Investigations, and Treatment of FCPD

Clinical features	Investigations	Treatment
Recurrent abdominal pain: Often beginning in childhood and preceding diabetes onset by years.	*Laboratory tests*: Markedly elevated plasma glucose and HbA1c. Pancreatic function tests demonstrate exocrine insufficiency.	*Glycemic control:* Most require insulin therapy; oral agents are usually insufficient.
Steatorrhea: Due to exocrine pancreatic insufficiency, causing oily, foul-smelling stools.	*Imaging*: Abdominal X-ray, ultrasound, or CT scan reveals large, discrete pancreatic calculi and ductal dilation.	*Exocrine insufficiency*: Pancreatic enzyme supplementation, low-fat diet, and supplementation with fat-soluble vitamins (A, D, E, K)
Diabetes mellitus: Usually insulin-requiring, with poor glycemic control but a low tendency for ketosis.	*Exclusion of other causes:* History of alcohol abuse or other causes of chronic pancreatitis should be ruled out.	*Pain management:* Mostly analgesics; in select cases, surgery for intractable pain or stone removal.
Weight loss and malnutrition are common due to chronic malabsorption.	*Genetic studies:* Mutations in genes such as SPINK1 may be present but are not routinely assessed (71).	*Complication surveillance:* Regular screening for microvascular complications, hypoglycemia unawareness, pancreatic malignancy (4,71).
Physical findings: Low BMI is typical, but some may have normal or increased BMI	*Glycemic monitoring:* Continuous glucose monitoring can assess glycemic variability (71).	*Prognosis:* Early diagnosis and comprehensive care improve outcomes, poor compliance for socioeconomic reasons is a challenge (70).
Complications: High rates of microvascular (retinopathy, nephropathy, neuropathy), less frequently macrovascular complications. Increased risk of pancreatic carcinoma.		

Hypoglycemia unawareness: Up to 75% due to cardiac autonomic neuropathy (71).		

Ketosis-Prone Diabetes (KPD)

DEFINITION

KPD comprises a heterogeneous condition characterized by unprovoked or minimally provoked DKA in individuals lacking autoimmune markers of T1DM, who may regain insulin independence after the acute episode. The Aβ classification system stratifies diabetes based on the presence of autoantibodies (A) and beta-cell functional reserve (β). This yields four subtypes, each with distinct clinical implications (Table 3). The most typical KPD phenotype is A−β+, characterized by negative autoantibodies and preserved β-cell function (72).

KPD can be further classified into subtypes based on the nature of the DKA trigger: a) Spontaneous KPD refers to cases in which DKA occurs without an evident precipitating factor; b) Provoked KPD, on the other hand, is associated with identifiable stressors such as infections, trauma, corticosteroid use, or acute pancreatitis (73). Patients with spontaneous KPD are more likely to demonstrate true β-cell dysfunction, whereas provoked cases may experience temporary metabolic decompensation due to stress-induced insulin resistance.

Table 3. Aβ Classification System for KPD

Subtype	Autoantibodies	β-cell function	Description
A+β−	Positive	Absent	Classic T1DM
A+β+	Positive	Preserved	Slowly progressive T1DM or latent autoimmune diabetes in adults
A−β−	Negative	Absent	Idiopathic diabetes (insulin-requiring)
A−β+	Negative	Preserved	True ketosis-prone diabetes

EPIDEMIOLOGY

Initial descriptions of KPD emerged from African American and sub-Saharan African populations, where the A−β+ phenotype was relatively common. Studies from Nigeria, Ghana, and Cameroon revealed that a significant proportion of patients with DKA did not require long-term insulin with recovery of endogenous insulin secretion (74). The prevalence of islet autoantibodies was low, and beta-cell recovery was noted in 70–80% of cases within a year. In India, similar cohorts could discontinue insulin within 3-6 months and maintain euglycemia with lifestyle measures and oral glucose-lowering agents (75).

PATHOGENESIS

The pathogenesis of KPD is complex, involving transient suppression of beta-cell function, significant insulin resistance, and the interplay of metabolic and inflammatory stressors. Several mechanisms have been proposed to explain the initial suppression of insulin secretion. Severe glucotoxicity and lipotoxicity can impair β-cell responsiveness. Elevated free fatty acids and ketone bodies may induce oxidative stress and mitochondrial dysfunction, leading to temporary beta-cell failure. Endoplasmic reticulum stress and cytokine-mediated inflammation (e.g., IL-1β, TNF-α) have also been implicated. Furthermore, hypophosphatemia during DKA may impair insulin

synthesis. Metabolomic and metabolic flux analyses provide insights into the pathophysiological underpinnings of KPD (76). The studies showed significant dysregulation in amino acid metabolism, mitochondrial substrate flux, and increased reliance on anaerobic glycolysis. Metabolic recovery post-DKA restored mitochondrial function and normalized oxidative pathways.

CLINICAL FEATURES

KPD commonly affects middle-aged men of African, Hispanic, or South Asian descent, who are usually overweight or obese. A strong family history of T2DM may exist. Presentation is with acute DKA, in the absence of any prior history of diabetes (77). The clinical features vary with the Aβ subtype, with the A−β+ subtype showing the most potential for remission.

There are differences between cohorts from India and Africa. Individuals from India tend to be leaner, with lower BMI despite central adiposity, and often present with higher HbA1c levels. In some cases, C-peptide recovery is delayed or incomplete, necessitating prolonged insulin therapy. The lower rate of complete insulin independence from India could be reflect ethnic, genetic, or nutritional influences (75).

INVESTIGATIONS

The diagnosis of KPD includes acute and long-term assessment of metabolic parameters and pancreatic function. At initial presentation, standard investigations for DKA should include plasma glucose, arterial pH, blood and urinary ketones, serum osmolality, and anion gap. In the subacute phase, the tests used to classify and guide therapy are summarized in Table 4.

Table 4. Investigations to Establish the Diagnosis of KPD

Investigation	Purpose
Glycated hemoglobin	Estimate duration of hyperglycemia
C-peptide (fasting/stimulated)	Assess β-cell reserve
GAD65, IA-2, ZnT8 antibodies	Evaluate autoimmune status
HOMA-IR	Quantify insulin resistance
Liver, renal and lipid profile	Assess metabolic comorbidities
Genetic screening (if atypical)/ CT abdomen	Rule out MODY/FCPD

TREATMENT AND LONG-TERM OUTCOMES

Initial management of KPD follows standard DKA protocols, including intravenous fluids, insulin, and electrolyte replacement. After stabilization, individuals are usually maintained on basal–bolus insulin with periodic C-peptide assessment. In those with preserved β-cell function (A−β+ subtype), insulin can be tapered over weeks to months. Oral glucose-l lowering agents may be introduced once ketone clearance is achieved and β-cell function is adequate. Lifestyle measures remain integral. Long-term studies indicate that up to 50% of A−β+ KPD cases maintain insulin independence at 5 years, although relapse may occur, particularly with infections or corticosteroid exposure (78). Indian studies have reported comparable remission rates but demonstrate a higher frequency of infection-related relapses. HLA-typing and genotyping may help predict the likelihood of remission and relapse (75).

Maturity Onset Diabetes of the Young (MODY)

MODY is a monogenic, autosomal dominant form of diabetes characterized by early-onset hyperglycemia, preserved β-cell function, and absence of autoimmunity (79,80). It accounts for 1–5% of cases of diabetes but is frequently misdiagnosed as T1DM or T2DM. Encompassing at least 14 genetic subtypes, the most common forms are HNF1A-MODY (MODY 3), marked by sulfonylurea sensitivity and progressive β-cell decline; and GCK-MODY (MODY 2), which causes mild stable fasting hyperglycemia often not requiring treatment (81). Other notable types include HNF4A-MODY (MODY 1), affecting insulin secretion and lipids, and HNF1B-MODY (MODY 5) with renal cysts. The subtypes of MODY are summarized in Table 5. For detailed discussion, readers are referred to the chapter "Diagnosis and Clinical Management of Monogenic Diabetes" of Endotext (79).

Table 5. MODY Subtypes with Genetic Mutations Involved

MODY Subtype	Gene	Pathophysiology	Management
MODY 1	HNF4A	Transcription factor defect	Sulfonylureas, insulin
MODY 2	GCK	Glucose-sensing defect	Usually no treatment
MODY 3	HNF1A	Transcription factor defect	Sulfonylureas, GLP-1 RA, insulin
MODY 4	PDX1	Beta-cell dysfunction	Diet, OADs, insulin
MODY 5	HNF1B	Multisystem involvement	Insulin, renal care
MODY 6	NEUROD1	Beta-cell dysfunction	Diet, OADs, insulin
MODY 7	KLF11	Beta-cell dysfunction	OADs, insulin
MODY 8	CEL	Protein misfolding	OADs, insulin
MODY 9	PAX4	Beta-cell differentiation defect	Diet, OADs, insulin
MODY 10	INS	Insulin biosynthesis defect	Diet, OADs, insulin
MODY 11	BLK	Insulin secretion defect	Diet, OADs, insulin
MODY 12	ABCC8	Ion channel defect	Sulfonylureas
MODY 13	KCNJ11	Ion channel defect	Sulfonylureas
MODY 14	APPL1	Signal transduction defect	Diet, OADs, insulin

Lipodystrophic Diabetes

Lipodystrophic diabetes represents a rare form of severe insulin-resistant diabetes resulting from partial or generalized loss of adipose tissue, leading to ectopic fat deposition, hepatic steatosis, and hypertriglyceridemia. Generalized forms present in infancy with near-total fat loss, muscular hypertrophy, hepatomegaly, and acromegaloid features, while partial lipodystrophy (e.g., Dunnigan-type) manifests at puberty with limb and gluteal fat loss but facial and cervical fat accumulation. The genetic alterations and mechanisms of hyperglycemia in lipodystrophy syndromes are outlined in Tables 6 and 7. For detailed discussion, readers are referred to the chapter "Lipodystrophy Syndromes: Presentation and Treatment" of Endotext (82).

Table 6. Generalized and Partial Lipodystrophy Syndromes with Genes and Inheritance			
Type	**Syndrome**	**Gene(s) Involved**	**Inheritance**
Generalized	CGL1	AGPAT2	Autosomal Recessive
Generalized	CGL2	BSCL2	Autosomal Recessive
Generalized	CGL3	CAV1	Autosomal Recessive
Generalized	CGL4	CAVIN1	Autosomal Recessive
Partial	FPLD2 (Dunnigan)	LMNA	Autosomal Dominant
Partial	FPLD3	PPARG	Autosomal Dominant
Partial	FPLD4	PLIN1	Autosomal Dominant
Partial	FPLD5	CIDEC	Autosomal Recessive
Partial	AKT2-related	AKT2	Autosomal Dominant
Partial	LIPE-related	LIPE	Autosomal Recessive
Partial	MFN2-related	MFN2	Autosomal Recessive
Progeroid	Hutchinson-Gilford Progeria	LMNA	De Novo
Progeroid	Mandibuloacral Dysplasia	LMNA, ZMPSTE24	Autosomal Recessive
Progeroid	Werner Syndrome	WRN	Autosomal Recessive
Progeroid	MDPL	POLD1	De Novo

Table 7. Mechanisms of Hyperglycemia in Lipodystrophy	
Mechanism	**Explanation**
Lipoatrophy	Inability to store triglycerides in adipocytes leads to ectopic fat deposition in liver, muscle, and pancreas.
Leptin Deficiency	Leads to hyperphagia, hepatic steatosis, and insulin resistance.
Adiponectin Deficiency	Reduces insulin sensitization and enhances hepatic gluconeogenesis.
Ectopic Fat Accumulation	Lipotoxicity impairs insulin action in muscle and liver and suppresses β-cell function.
Pro-inflammatory State	TNF-α and IL-6 levels are elevated, promoting insulin resistance.

Other Atypical Forms of Diabetes

Atypical phenotypes, including rare syndromic forms, occur worldwide and exhibit similar features in tropical regions. Mitochondrial diabetes results from mtDNA mutations, most notably the A3243G mutation in MT-TL1, causing defective mitochondrial protein synthesis, impaired β-cell energy metabolism, and features such as sensorineural hearing loss and cardiomyopathy. Neonatal diabetes mellitus (NDM), a distinct form of monogenic diabetes, usually presents in the first six months of life. NDM may be transient or permanent, and arise from mutations in KCNJ11, ABCC8, or INS genes. Wolfram syndrome (DIDMOAD), an autosomal recessive disorder caused by mutations in the WFS1 gene, induces β-cell apoptosis via endoplasmic reticulum stress, leading to early-onset insulin-dependent diabetes accompanied by optic atrophy, deafness, and diabetes insipidus. The atypical forms of diabetes are discussed in the

chapter titled “Atypical Forms of Diabetes” in Endotext (83).

CLINICAL IMPLICATIONS AND THERAPEUTIC STRATEGIES IN LEAN DIABETES

The pathophysiology of lean diabetes is characterized by impaired beta-cell function, ectopic fat accumulation, sarcopenia, and developmental influences. These mechanisms differ and necessitate a shift away from conventional strategies for T2DM, where weight reduction and insulin sensitization remain the primary focus. Management should be individualized to target the distinctive metabolic and physiological features of lean diabetes. Table 8 summarizes the key variants of lean diabetes in the tropics.

Table 8. Summary Table of Key Differentials of Lean Non-Autoimmune Diabetes in Adults

Feature	FCPD	MRDM / Type 5 DM	KPD	MODY	Lipodystrophic Diabetes
Demographics	Onset <30–40 yrs; tropics	Adolescents/ young adults in LMICs	Young adults; African/Asian	Onset <25–35 yrs	Adolescents/young adults; congenital/acquired
Family History	Absent	Absent	Absent	Strong (AD , three-generation pattern)	Variable, familial forms
Nutritional History	Low nutrition possible	Early malnutrition, stunting	Not contributory	Normal	Normal or partial loss of fat
BMI	Lean	Underweight, low birth weight	Lean	Lean/normal	Low BMI, lack of subcutaneous fat
Onset	Gradual, recurrent pancreatitis	Gradual	Acute ketosis /DKA at onset	Gradual, mild hyperglycemia	Variable, insulin-resistant
Ketosis	Rare, stress-related	Rare	Present at onset	Absent usually	Rare, possible if insulinopenic
C-Peptide	Low to low-normal	Low	Low initially, recovers	Preserved	High initially, declines
Autoantibodies	Negative	Negative	Negative	Negative	Negative
Insulin Resistance	Absent	Absent	Absent	Absent	Marked despite leanness
Pancreatic Exocrine Dysfunction	Present (steatorrhea	Possible mild insufficiency	Absent	Absent	Absent

	, deficiencies)				
Imaging Findings	Pancreatic calcifications, atrophy	Possible atrophy, small size	Normal	Normal, MODY-5 – renal/urinary tract anomalies	Normal, fatty liver
Typical Biochemical Features	Brittle glycemia, low insulin	Low insulin need	Initial insulin dependence	Stable HbA1c, mild hyperglycemia	Severe IR, high triglycerides
Genetics	SPINK1, CFTR in some	None defined	None defined	HNF1A, HNF4A, GCK and others	LMNA, PPARG (familial forms)and others
Treatment	Insulin + pancreatic enzyme replacement	Low-dose insulin, secretagogues, nutrition	Insulin then taper	Sulfonylureas effective	High-dose insulin ± leptin
Prognosis	Progressive metabolic complications	Poor nutrition complicates	Variable, remission possible	Depends on variants	Progressive metabolic complications

Diagnostic Challenges and Misclassification

Lean diabetes is frequently misclassified as T1DM or LADA due to early insulin dependence. Key differentiators include the absence of ketosis, family history, and preserved C-peptide levels. Autoantibody testing (GAD65, IA-2, ZnT8) helps exclude autoimmune diabetes. Fasting C-peptide–based algorithms may provide additional information regarding insulin secretory capacity.

Individualized Pharmacotherapy

Given predominant β-cell dysfunction, insulin remains the predominant therapy in the majority of cases of lean diabetes. Agents that enhance insulin secretion, such as sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonists, can be effective in some variants, such as KPD and MODY. Sulfonylureas remain low-cost options, though the risk of hypoglycemia and durability are concerns. Metformin, despite its limited insulinotropic effect, offers pleiotropic benefits, including reduced hepatic fat and improved endothelial function. Early insulin is indicated in severe hyperglycemia or low C-peptide states, with periodic reassessment for endogenous recovery.

Nutritional Interventions

Calorie restriction is inappropriate; the goals are to maintain lean mass and prevent sarcopenia. Diets should emphasize adequate protein, whole grains, legumes, and healthy fats while limiting refined carbohydrates common in tropical countries. Monitoring and correction of micronutrient deficiencies (vitamin B12, vitamin D, and iron) are essential for metabolic health.

Role of Physical Activity and Muscle Preservation

Exercise should focus on resistance and strength training to improve insulin sensitivity and muscle mass. Combining aerobic exercise enhances both metabolic and cardiovascular health.

Screening and Public Health Implications

BMI-based screening might not detect lean diabetes. Waist circumference, waist-to-height ratio, and triglyceride-to-HDL ratios offer better sensitivity. Screening thresholds must be lowered for South Asians and Africans, who develop diabetes at a lower BMI. Early-life interventions targeting maternal nutrition and childhood growth are critical, alongside community programs that emphasize muscle preservation and metabolic screening regardless of weight.

Precision Medicine

Future approaches integrating genomic, epigenetic, metabolomic, and microbiome data can stratify lean diabetes into mechanistic types (e.g., insulin secretory vs. inflammatory), enabling personalized treatment. Precision strategies hold the promise of improved risk prediction, therapeutic targeting, and better outcomes in this heterogeneous group of disorders.

CONCLUSION

Lean non-autoimmune diabetes is a distinct and multifaceted entity marked by loss of beta-cell function with additional influence of visceral fat, sarcopenia, and early-life undernutrition. Correctly recognizing subtypes such as MRDM, FCPD, KPD, and MODY helps avoid misclassification with T1DM and T2DM. Insulin remains the mainstay of treatment, supported by balanced nutrition and strength training to improve lean mass. Future progress depends on adopting ethnicity-specific BMI thresholds, enhancing understanding of body composition variability, and applying genetic and metabolic insights to refine diagnosis and optimize management.

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