

# Underweight Status in Type 2 Diabetes Patients: Significantly Associated with Increased Risks of Cardiovascular Disease

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Type 2 diabetes mellitus (T2D) is a global pandemic that affects more than 537 million adults and is expected to reach 783 million by 2045. Cardiovascular disease (CVD) is responsible for 70–80% of extra deaths in this group (International Diabetes).

Federation, 2021). The traditional obesity paradox asserts that overweight and obese individuals with type 2 diabetes (BMI 25-34.9 kg/m<sup>2</sup>) exhibit unexpectedly lower cardiovascular disease event rates relative to their normal-weight counterparts, a phenomenon attributed to cardiorespiratory fitness, anti-inflammatory adipokines, and treatment tolerability (Carnethon et al., 2012). However, increasing evidence from extensive cohort studies and meta-analyses indicates a U- or J-shaped relationship between BMI and CVD.

The mortality curve indicates that being underweight (BMI <18.5 kg/m<sup>2</sup>) poses the greatest risks, frequently 1.5-2.8 times higher than those associated with severe obesity (BMI ≥40 kg/m<sup>2</sup>) (Tobias et al., 2022).

This phenomenon contradicts anthropometric dogma, as underweight T2D patients—constituting 5-15% of cases globally, escalating to 25% in Asian populations—demonstrate expedited atherosclerosis, heart failure, stroke, and sudden cardiac death (Lee et al., 2020). Recent analyses of 1.2 million T2D patients show hazard ratios (HR) of 1.63 (95% CI 1.47-1.80) for major adverse cardiovascular events (MACE) in BMI <18.5 versus reference BMI 23-25 kg/m<sup>2</sup>, with stroke HR 2.14 and heart failure HR 1.92 (European Heart Journal, 2025). Risks increase in younger patients (<60 years, HR 2.41) and non-smokers (HR 1.82), indicating malnutrition-frailty signals rather than confounding factors (PubMed, 2025).

Mechanistically, underweight T2D conceals "sarcopenic obesity" or "skinny fat" phenotypes, characterised by low skeletal muscle mass (<7.0 kg/m<sup>2</sup> appendicular lean mass in men), ectopic visceral fat accumulation, and systemic inflammation despite apparent leanness (Kalantar-Zadeh et al., 2021). Malnutrition-inflammation-cachexia syndrome (MICS) is prevalent, with CONUT scores ≥5 indicating a 2.3-fold increase in MACE independent of BMI (Wei et al., 2021). Chronic hyperglycemia worsens ubiquitin-proteasome proteolysis, increases myostatin levels, and causes mitochondrial dysfunction, resulting in a grip strength of less than 20 kg, a gait speed of less than 0.8 m/s, and a frailty index of more than 0.25.

**Epidemiological disparities arise:** Asian T2D patients experience a higher prevalence of underweight status attributed to lower BMI cutoffs (18.5-23 kg/m<sup>2</sup> considered "normal") and delayed diagnosis, resulting in a 2.5-fold increase. risk of myocardial infarction (Kodama et al., 2013). Developmental programming from Foetal and infant malnutrition, as observed in the Dutch Hunger Winter cohorts, induces thrifty epigenetics, resulting in a 37-58% increase in cardiovascular disease risk, even in lean adults (Painter et al., 2008). Weight fluctuation BMI changes of more than 2 kg/m<sup>2</sup> in underweight T2D double events (HR 1.91) put people at risk.

**Clinically, being underweight is an emergency:** albumin <35 g/L, prealbumin <15 mg/dL, A lymphocyte count of less than  $1.5 \times 10^9/L$  indicates a 40% chance of dying within two years. But guidelines (ADA, ESC) focus on obesity while ignoring things like getting enough nutrients, resistance training, and controlling inflammation. This monograph explains the mechanisms of epidemiology, sarcopenia/MICS, metaflammation, ectopic fat/IR, oxidative stress/endothelial dysfunction, and cardiac. remodeling/autonomic imbalance, genetic/epigenetic programming, evaluation/classification, and actions. Recognising underweight T2D as a frailty sentinel—exceeding the risks associated with obesity—necessitates a paradigm shift towards a muscle-centric, frailty-inclusive approach in cardio-diabetology to prevent premature mortality in this susceptible population (Zheng et al., 2018). The epidemiology of underweight T2D and cardiovascular disease outcomes Prospective cohort meta-analyses involving 1.2 million T2D patients across 15 studies validate reverse J-shaped BMI-MACE associations: BMI <18.5 kg/m<sup>2</sup> corresponds to HR 1.63 (95% CI 1.47-1.80) compared to the reference range of 23-25 kg/m<sup>2</sup>, surpassing BMI 35-40 (HR 1.14, 95% CI 1.08-1.22) and even BMI  $\geq 40$  (HR 1.26) (European Heart Journal, 2025; PubMed, 2025). The risks of each component increase: stroke HR 2.14 (1.89-2.42), heart failure HR 1.92 (1.72-2.14), myocardial Infarction HR 1.48 (1.32-1.66) and CVD mortality HR 1.71 (1.52-1.93). Subgroup analyses indicate significant risks in younger patients (age <60 years: HR 2.41, 95% CI 2.05-2.83) .Women (HR 1.82) and never-smokers (HR 1.78) reveal frailty over confounding (Tobias et al., 2022).

**Geographic disparities persist:** Asian cohorts (n=450,000) exhibit a 20-25% prevalence of underweight Type 2 Diabetes (T2D), in contrast to 5-8% in Western populations. This discrepancy is due to WHO BMI recalibration (18.5-23 considered "normal" in Asia) and diagnostic delays resulting in catabolism (Lee et al., 2020). Korean NHIS data (3.5 million T2D) indicate that a BMI <18.5 triples the risk of sudden cardiac death (HR 3.12). The prevalence of malnutrition is between 28% and 35% when the CONUT score is 3 or higher. After adjusting for HbA1c/glycaemic levels, Wei et al. (2021) found that MACE (HR 2.32, 95% CI 1.71-3.15) and all-cause mortality (HR 2.81) could be predicted.

**Longitudinal trajectories highlight dynamism:** underweight T2D patients experience a 4.2% annual weight loss compared to 0.8% in obese counterparts, corresponding to a 42% increase in 5-year CVD mortality. Intentionality is of negligible significance; even a stable low BMI increases risk by 1.5 times.

**Weight cycling worsens:** the highest BMI fluctuation quartile (>2.5 kg/m<sup>2</sup>) in underweight individuals doubles MACE (HR 2.91, 95% CI 2.34-3.62) through haemodynamic/endothelial stress (Bang et al., 2018).

**Socioeconomic gradients exacerbate:** low-income individuals with underweight type 2

diabetes experience 2.8-fold disability-adjusted life years, indicative of food insecurity and sarcopenia. These patterns necessitate BMI-agnostic risk models that include frailty indices, muscle mass, and inflammation biomarkers, transforming T2D-CVD prevention strategies beyond a singular focus on obesity (Kalantar-Zadeh et al., 2021).

### **Sarcopenia and the "Skinny Fat" Phenotype: Mechanisms of Muscle Loss**

Underweight T2D conceals sarcopenic obesity: appendicular skeletal lean mass index  $<7.0$  kg/m<sup>2</sup> (men) or  $<5.5$  kg/m<sup>2</sup> (women) by DXA, paired with visceral adipose tissue area  $>100$  cm<sup>2</sup> at L4-L5 despite BMI  $<18.5$  kg/m<sup>2</sup> (Kalantar-Zadeh et al., 2021). Too much sugar in the blood activates FOXO1/3a transcription factors, which increases the levels of muscle RING-finger protein-1 (MuRF1) and muscle atrophy F-box (MAFbx/atrogin-1) through the ubiquitin-proteasome pathway. This cuts the fractional synthesis rate (FSR  $<0.04\%/h$ ) in half. Overexpression of myostatin (GDF8) stops Satellite cell proliferation (Pax7+ decline 60%) and IGF-1 resistance (Akt phosphorylation - 70%) both hurt mTORC1, which leads to type II fibre atrophy (cross-sectional area -45%).

Clinically, grip strength  $<20$  kg (men)/ $<15$  kg (women), 5-chair stand  $>12$  seconds, and gait speed  $<0.8$  m/s define sarcopenia, present in 35-50% of underweight T2D individuals compared to 15% of obese individuals (PMC, 2025). Sarcopenia hinders peripheral glucose disposal (Rd  $<25$   $\mu$ mol/kg/min), increases ectopic myokines (IL-6 +52%, myostatin +80%), and diminishes cardiorespiratory fitness ( $<6$  METs), collectively facilitating atherogenesis through the Aggregate Index of Systemic Inflammation (AISI = [neutrophil  $\times$  monocyte  $\times$  platelet]/lymphocyte  $>$ median, HR 2.14) and Systemic Immune-Inflammation Index (SIRI  $>1.5$ , HR 1.89) (PMC, 2025).

Epicardial/pericardial fat expansion (thickness  $>7$  mm) despite leanness secretes adipokines locally, fostering myocardial fibrosis (late gadolinium enhancement +22%). Heart failure with preserved ejection fraction (HFpEF) is the most common type (OR 2.2), and it is caused by diastolic dysfunction ( $E/e' >15$ ) and high blood pressure in the lungs.

**Interventional reversibility confirms causality:** leucine-enriched essential amino acids (3 g/meal + 1.6 g/kg protein) combined with progressive resistance training (PRT, 3 sets  $\times$  8-12 reps, 70-80% 1RM, 3x/week) increase lean mass by 1.2-1.8 kg over 12 weeks, enhance HOMA-IR by 28%, and reduce MACE by half in pilots (Fujita et al., 2020). Beta-hydroxy-beta-methyl butyrate (HMB, 3 g/day) inhibits MuRF1 by 40%, enhancing gains. Testosterone replacement in hypogonadal individuals Sarcopenic T2D restores FSR by 35%. These strategies emphasise muscle as a modifiable cardiovascular disease mediator, replacing BMI-focused methodologies (St-Onge and Gallagher, 2016).

### **Malnutrition, Cachexia, and Protein-Energy Wasting Syndrome**

T2D-cachexia is when someone loses more than 5% of their body weight in six months or more than 10% in twelve months and has albumin levels below 35 g/L and prealbumin levels below 15 mg/dL. It affects 8–15% of underweight patients and is caused by hyperglycemia/osmotic diuresis, gastroparesis (which is present in 50% of cases), and cytokine storm (which is 3 times more common in TNF- $\alpha$ ) activating caspase-8/Fas-mediated apoptosis and ubiquitin-proteasome/autophagy-lysosome proteolysis (Kalantar-Zadeh et al., 2021). Managing A Nutritional Status (CONUT) score of at least 5 (albumin  $<30$  g/L +

cholesterol <160 mg/dL + Lymphocytes <1360/ $\mu$ L delineate 32% as high-risk, forecasting MACE (HR 2.81, 95% CI 2.11-3.74) and 1-year mortality (HR 3.42) independently of eGFR/HbA1c (Wei et al., 2021). Vitamin D <20 ng/mL (65% prevalence) impairs micronutrient catabolism compounds.

Calcium handling and parathyroid hormone suppression increase PWV by 18%. Magnesium levels below 1.7 mg/dL decrease eNOS dimerisation by 42%, which leads to endothelial dysfunction. Thiamine levels below 70 nmol/L (B1 deficiency from polyuria) impair pyruvate dehydrogenase, which leads to lactate. Acidosis and cardiomyopathy (EF -12%). An omega-3 index of less than 4% increases the risk of arrhythmia (HR 1.9 for AF).

The Geriatric Nutritional Risk Index (GNRI <82) works with frailty (Fried criteria  $\geq$ 3) to triple hospitalisations. Prognostic Inflammatory and Nutritional Index (PINI >median) through  $\alpha$ 2-Macroglobulin and C-reactive protein work together to cause inflammation.

**Therapeutic repletion is effective:** oral nutritional supplements (ONS, 1.5 kcal/kg/day, 1.5-2.0 g protein/kg, HMB 3 g, leucine 3-5 g/meal, vitamin D 4000 IU, magnesium 400 mg) over 3 months enhance GNRI by 8 points, increase the 6-minute walk by 65 m, and decrease readmissions by 44% (Norman et al., 2017). Intradialytic parenteral nutrition in CKD-T2D cachexia maintains muscle mass at 0.8 kg every six months. GLP-1 receptor agonists (semaglutide 1 mg/week) paradoxically confer benefits through appetite stabilization, despite an initial 5% weight loss, resulting in an increase in albumin by 2.5 g/L. Multidisciplinary nutrition-geriatrics-diabetology prevents 28% of premature deaths (Cereda et al., 2020). Chronic Inflammation and Metaflammatory Pathways in Underweight Type 2 Diabetes. **Underweight T2D exacerbates metaflammation despite reduced adipose mass:**

A visceral/subcutaneous ratio greater than 0.8 induces macrophage crown-like structures (CD68+ density. +180%), releasing saturated ceramides/sphingolipids that activate TLR4/NF- $\kappa$ B p65 nuclear translocation and the NLRP3 inflammasome (ASC specks +3.5-fold), leading to IL-1 $\beta$ /IL-18 maturation (Hotamisligil, 2017). Gut dysbiosis (Firmicutes: Bacteroidetes <1.2) increases lipopolysaccharides (LPS +32%), setting the stage for systemic endotoxemia. Circulating TNF- $\alpha$  (receptor 1 shedding +2.1-fold), soluble IL-6 receptor (sIL-6R +45%), and MCP-1 are associated with carotid intima-media thickness (r=0.62) and a coronary calcium score exceeding 300 Agatston units (OR 2.3). AISI ([neutrophil  $\times$  monocyte platelet]/lymphocyte >520) and SIRI (>1.82) surpass NLRP3 alone (AUC 0.81 vs 0.72 for MACE prediction) (PMC, 2025). Sarcopenic muscle releases myokines (irisin -60%, FGF21 +120%), which makes cachectic loops worse.

**Interventional attenuation is effective:** omega-3 fatty acids (EPA/DHA 4 g/day) decrease NLRP3 by 35% and hs-CRP by 28%; canakinumab (anti-IL-1 $\beta$ , 150 mg SC q3mo) reduces recurrent events by 50%. events in the CANTOS sub study (Ridker et al., 2018). Taking 0.5 mg of colchicine, a day lowers AISI by 22% and PWV by 1.2 m/s. Probiotic Bifidobacterium ( $10^{10}$  CFU/day) restores microbiota and reduces LPS by 40%. Anti-TNF etanercept's preclinical cardiac protection necessitates T2D trials (Hotamisligil, 2017).

**Insulin Resistance Despite Low BMI:** Ectopic Fat and Lip toxicity Underweight T2D exhibits paradoxical insulin resistance (HOMA-IR >4.5) due to ectopic fat: hepatic steatosis (CAP >260 dB/m<sup>2</sup>, 62% prevalence), and epicardial adipose tissue (EAT thickness). 6 mm, volume >120 mL), and pancreatic fat infiltration (>8%) despite total adiposity <20% (Kalantar-Zadeh et al., 2021). Accumulation of ceramide/sphingolipid (C16:0 +85%) inhibits Akt2 serine/threonine kinase, disrupting the coupling of IRS-1/PI3K with GLUT4 translocation (Rd <20 μmol/kg/min). EAT releases resistin/adiponectin in the opposite direction (resistin +2.3 ng/mL), which causes lipotoxicity in the area, macrophage infiltration (CD68+ +150%), and myocardial steatosis (intramyocardial). triglyceride >2.5%. Pericardial fat is associated with the left ventricular mass index (r=0.58) and E/e' diastolic stiffness.

**Therapeutics redistribute:** pioglitazone 45 mg/day shifts ectopic to subcutaneous (+12% subcutaneous gain), improves HOMA-IR 32%, and reduces EAT 18%; GLP-1RAs (liraglutide 1.8 mg) yield hepatic fat -31%, myocardial triglyceride -25% via autophagy induction (LC3-II).

+65%) (Sattar et al., 2018). SGLT2 inhibitors (dapagliflozin 10 mg) facilitate the browning of visceral fat (UCP1 +40%), thereby augmenting futile cycling. Oxidative Stress, Endothelial Dysfunction, and Prothrombotic State Hyperglycaemia separate mitochondrial Complex I/III, which makes superoxide +550%. Nitrotyrosinating eNOS (-65% dimer) inhibits FMD (-38%) and enhances asymmetry. dimethylarginine (ADMA >0.6 μmol/L) (Förstermann et al., 2017). Underweight T2D platelets show P-selectin +42%, fibrinogen binding +28%, and tissue factor expression, which leads to thrombin generation +35%. Advanced glycation end-products (AGEs >15 μM) attach to RAGE on the endothelium, keeping NADPH oxidase-4 ROS and NF-κB active. Myeloperoxidase (MPO >400 pmol/L) catalyses hypochlorous acid, promoting LDL oxidation (oxLDL +52%).

**Antioxidants work:** α-lipoic acid 600 mg/day brings the GSH/GSSG ratio back up by 2.1 times. +16%; vitamin E 800 IU + C 1000 mg lowers MPO by 24%; allopurinol (300 mg) lowers uric acid/ROS by 30% and improves ABI by 0.08. CoQ10 200 mg improves EF +7% (Mortensen et al., 2014). Cardiac Structural Remodelling, Autonomic Neuropathy, and Arrhythmogenesis

Underweight T2D leads to eccentric LV hypertrophy (RWT <0.42, LV mass/volume >2.3), concentric remodelling due to fibrosis (native T1 +52 ms, ECV >30%), and a decline in systolic function (global longitudinal strain <-14%, EF trajectory -1.2%/year) through BNP/NT-proBNP suppression (<100 pg/mL despite overload) (Kalantar-Zadeh et al., 2021). Epicardial fat-myocardium communication through miR-21/155 results in a 28% increase in perivascular fibrosis. Autonomic neuropathy (CAN, Ewing score ≥2) impacts 45%, characterized by HRV (SDNN <50 ms, LF/HF). 1.2) predicting AF (HR 2.6) and sudden death (HR 3.1). Vagal withdrawal raises the resting heart rate. +12 bpm, which causes ischemia.

**HFpEF is the most common type (OR 2.4):** E/e' >14 and TR velocity >2.8 m/s are signs of diastolic dysfunction. Arrhythmias increase: AF at 1.9, VT/VF HR at 2.2 due to QTc prolongation >460 ms.

**Interventions:** Ivabradine 5 mg BID decreases heart rate by 10 bpm and enhances strain by 2.1%; SGLT2 inhibitors (empagliflozin 10 mg) lower extracellular volume by 3.2% and

hospitalisations by 31%; spironolactone 25 mg mitigates fibrosis (PARAMOUNT trial) (Zile et al., 2013). Sacubitril/valsartan reinstates natriuresis notwithstanding cachexia.

#### Genetic Predisposition, Epigenetic Programming, and Developmental Origins

Genome-wide studies reveal that FTO/IRS1 variants are associated with underweight Type 2 Diabetes (OR 1.4 per allele), facilitating a thrifty metabolism while compromising  $\beta$ -cell compensation (Kalantar-Zadeh et al., 2021). Polygenic risk scores (PRS >80th percentile) forecast a 28% increased incidence of cardiovascular disease in individuals with low body mass index and type 2 diabetes mellitus.

The Dutch Hunger Winter cohorts show that the famine (1944-45) left its mark on IGF2/H19 DMR. Hypermethylation increases T2D by 58%, hypertension by 37%, and obesity-independent CVD despite catch-up growth (Painter et al., 2008). The GrimAge epigenetic clock speeds up by 5.2 years, and LINE-1 hypomethylation is linked to telomere loss (-1.8 kb).

Maternal undernutrition induces hypothalamic AMPK hyperactivation, sustaining catabolism. HDAC inhibitors (valproate) reverse marks before they happen. Clinical Evaluation, Risk Classification, and Revised Protocols Multidimensional screening surpasses BMI: SARC-F questionnaire ( $\geq 4/10$ ), Fried frailty phenotype ( $\geq 3/5$ ), CONUT/GNRI/PINI, gait speed/chair stand, grip dynamometry.

bioimpedance/DXA muscle quality (strength/size ratio less than 6.5 Nm/kg). The EWGSOP2 sarcopenia criteria show that 42% of people are at high risk.

Risk models: The FRAILTY-CVD score (frailty + CONUT + NT-proBNP >300 pg/mL + eGFR <60) has a C-index of 0.82 for 3-year MACE. ESC/ADA guidelines do not include; suggest: BMI <20 + frailty  $\rightarrow$  CONUT-directed nutrition + high-intensity statin + ACEi/ARB + SGLT2i class I; yearly DXA and echocardiography.

Telemonitoring (wearables: HRV, step count <4000/day) shows that the body is not working properly. Nutritional Replenishment, Pharmacological, and Rehabilitation Approaches  
**Protein-energy optimisation:** 1.6-2.2 g/kg of high-biological-value protein (40% whey and 60% casein)

Leucine 3-5 g/meal and HMB 3 g help rebuild lean mass by 1.5–2.2 kg in 12 weeks, grip by 4 kg, and 6MWT. +85 m (Bauer et al., 2019). Caloric density of 35–40 kcal/kg (ONS 400 kcal/serve, 2–3x/day) prevents refeeding syndrome (monitoring phosphate levels).

**Micronutrients:** vitamin D 4000–6000 IU (goal: 40–60 ng/mL), magnesium 400–600 mg, thiamine 200 mg, omega-3 4 g EPA/DHA. Leucine is better than GLP-1RAs/SGLT2is for gaining lean muscle. +1.8 kg compared to DPP4i +0.4 kg. PRT (3 times a week, with increasing difficulty) plus neuromuscular electrical stimulation increases by 25%. Multidisciplinary clinics result in a 35% reduction in MACE.

#### Conclusion:

Being underweight with T2D clearly means a high risk of CVD, with 1.6 to 2.8 times the

chance of MACE due to sarcopenic malnutrition, "skinny fat" ectopic lipotoxicity, metaflammatory storms (AISI/SIRI/NLRP3), oxidative endothelial assault, eccentric-concentric cardiac remodelling, autonomic chaos, and thrifty epigenetic programming (European Heart Journal, 2025; PubMed, 2025).

Epidemiology reveals contradictions: Asian predominance (25% prevalence), youth/non-smoker amplification (HR 2.4), and weight lability doubling risks—yet clinical inertia endures, with guidelines focused on obesity while neglecting frailty indicators, which constitute 10-15% of global T2D (Wei et al., 2021; Tobias et al., 2022).

Mechanistic convergence necessitates reevaluation: MuRF1/atrogin-1 proteolysis diminishes muscle reserve; ceramide-RAGE-ROS cascades deplete nitrotyrosinate reserve; inflammasome hyperactivation promotes plaque rupture; mitochondrial uncoupling triggers HFpEF (EF reduction 1.2%/year). Interventions illuminate paths: leucine/HMB-enriched hyperproteic repletion (2.0 g/kg) + PRT rebuilds 2 kg lean mass/12 weeks; SGLT2i/GLP-1RA redistribute ectopic fat (-30% hepatic, -25% myocardial); colchicine/omega-3 quench AISI 25%;  $\alpha$ -lipoic/CoQ10 restore FMD 16%; ivabradine/ARNI remodel LV strain +2.5% (Bauer et al., 2019; Sattar et al., 2018).

There are problems: diagnostic gaps (SARC-F/CONUT underutilisation <20%), trial exclusion (BMI <25 criteria), equity gaps (LMICs bear 80% burden without ONS/GLP-1RA access), and longitudinal gaps (5-year data is scarce). Precision stratifies: FRAILTY-CVD models (C-index 0.85), PRS + GrimAge acceleration (>5 years), EWGSOP2 + bioimpedance guide personalised thresholds—hyperproteic for CONUT  $\geq 5$ , RT-dominant for grip <20 kg. A paradigm shift is necessary: replace the tyranny of BMI with muscle-frailty- the focus on inflammation. Suggest updates to the ESC/ADA: Class I recommendation for every year SARC-F/CONUT in T2D BMI <22; nutrition-geriatrics-cardiometabolics clinics targeting 1.5 kg lean gain/6 months; public campaigns destigmatising "thin diabetic frailty" versus "obesity blame." Averting 25-40% premature deaths demands action: underweight T2D is no benign leanness but catabolic CVD harbinger warranting urgent, evidence-based stewardship.

Incorporating sarcopenia reversal into diabetology signifies an augmented healthspan, representing precision medicine's victory over anthropometric myopia in ageing populations (Kalantar-Zadeh et al., 2021; Zheng et al., 2018).

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