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Impact of Fat Distribution and Muscle Mass Phenotypes on Metabolism and Their Role in Subtyping T2DM

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Abstract

Background: *Type 2 diabetes mellitus (T2DM) is characterized by significant metabolic heterogeneity, requiring precise subtyping to optimize personalized management. While etiological classifications are foundational, they lack the granularity needed to predict diverse clinical trajectories.*

Objective: *This review elucidates the role of body composition phenotypes—specifically regional adiposity and skeletal muscle mass—as a framework for T2DM stratification.*

Synthesis*: We synthesized evidence regarding the pathophysiological cross-talk between adipose and skeletal muscle tissues. Adipose tissue modulates metabolism via lipotoxicity and systemic inflammation, while skeletal muscle governs glucose homeostasis through insulin-mediated uptake and myokine secretion. Crucially, the transition from regional fat distribution (visceral vs. gluteofemoral) to ectopic deposition (liver, pancreas) differentially impacts insulin resistance and beta-cell function. Dual-energy X-ray absorptiometry (DXA) is highlighted as a robust modality for precise phenotyping.*

Key Findings: *T2DM can be stratified into four distinct phenotypes: sarcopenic, simple obese, sarcopenic obese, and normal composition. Notably, the muscle-to-fat ratio often exhibits superior predictive value for cardiovascular and microvascular complications compared to solitary parameters.*

Conclusion: *Body composition-based phenotyping via DXA offers a scalable approach for T2DM subtyping. Integrating these anatomical markers into clinical practice facilitates targeted interventions and improves long-term metabolic prognoses.*

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Introduction

Diabetes mellitus is a chronic metabolic disease characterized by insulin deficiency or insulin resistance, driven by a complex interplay of genetic and environmental factors. It has increasingly emerged as a paramount threat to global public health. In 2021, the global prevalence of diabetes among adults aged 20–79 was estimated at 10.5% (536.6 million people) [1]. By 2022, the number of adults living with diabetes worldwide reached an estimated 828 million, with China accounting for the largest share of this global burden (approximately 148 million, range 103–202 million) [2]. Consequently, diabetes has become one of the leading causes of chronic disease-related mortality worldwide.

Diabetes is closely associated with complications such as cardiovascular disease, renal impairment, neuropathy, and retinopathy, with these associations being particularly pronounced in type 2 diabetes (T2DM). Consequently, there is an urgent need for more refined and individualized therapeutic strategies [3]. The prerequisite for achieving such precision and individualized treatment is the customization of therapeutic regimens centered on patients' specific phenotypes and individual characteristics—including islet beta-cell function, lipid profile, body fat distribution, and muscle mass [4, 3]. This necessitates the classification of patients, particularly those with T2DM, to implement tailored management plans. However, a universally applicable and widely implemented classification system for T2DM remains currently unavailable.

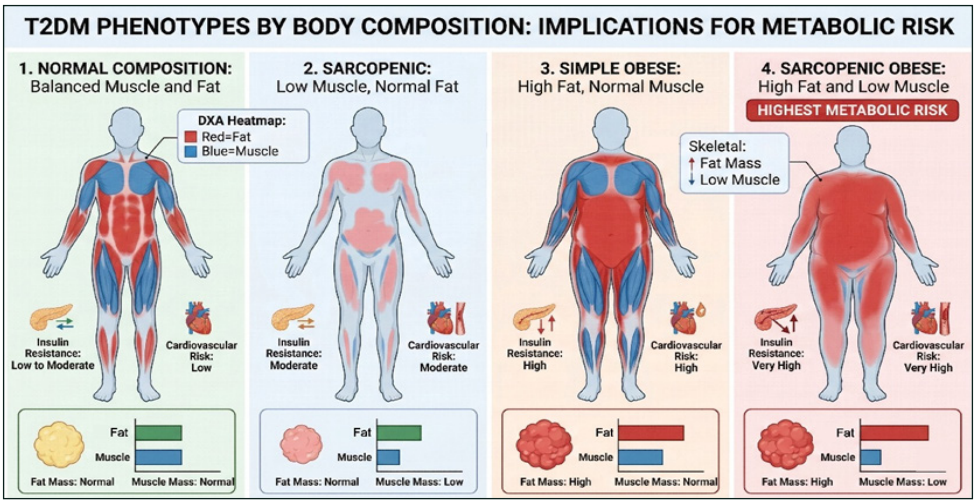

Figure 1:1. Normal Composition: Characterized by an optimal balance between skeletal muscle mass and adiposity.2. Sarcopenia: Defined by reduced muscle mass with preserved fat mass, associated with moderate insulin resistance and cardiovascular risk.3. Simple Obesity: Characterized by increased adipose tissue and preserved muscle mass, leading to high insulin resistance and cardiovascular risk.4. Sarcopenic Obesity: Defined by the concomitant reduction in muscle mass and expansion of adiposity, presenting the highest (very severe) levels of insulin resistance and cardiovascular risk.

Traditional Classifications of Diabetes and their Limitations

The most widely utilized classification system currently remains the one proposed by the World Health Organization (WHO) in 1999. This framework categorizes diabetes into type 1 diabetes, type 2 diabetes, specific types of diabetes, and gestational diabetes, primarily based on their distinct etiologies and pathophysiological characteristics. Type 1 diabetes mellitus (T1DM) is characterized by an absolute insulin deficiency, typically resulting from the immune-mediated destruction of pancreatic beta cells. In contrast, T2DM is defined by varying degrees of insulin resistance combined with a relative insulin secretory deficit

or a primary defect in insulin secretion coupled with resistance [5]. While this classification has historically assisted clinicians in diagnostic stratification and laid the groundwork for individualized treatment, ongoing research has revealed that this model increasingly struggles to meet the demands of contemporary precision medicine.

In 2019, the WHO updated the 1999 guidelines by removing sub-classifications of T1DM and T2DM and introducing "Hybrid forms of diabetes" and "Unclassified diabetes." The hybrid category encompasses Latent Autoimmune Diabetes in Adults (LADA) and Ketosis-Prone Type 2 Diabetes[6]. Nevertheless, for T2DM—a population characterized by an immense patient base and profound heterogeneity[7, 3]—an effective, practical classification method that can reliably guide clinical diagnosis and therapeutic decision-making is still lacking.

A review entitled "Metabolic Phenotypes and Step by Step Evolution of Type 2 Diabetes: A New Paradigm" proposes that the diagnosis and classification of T2DM should not rely solely on blood glucose levels. This paradigm categorizes the evolution of T2DM into three distinct phenotypes: (1) low levels of both fasting insulin and blood glucose; (2) normal tolerance levels for both insulin and glucose, with rare occurrences of ketosis; and (3) a T2DM spectrum encompassing four progressive stages of disease development. These stages include the "pre-pre-diabetes" stage (hyperinsulinemia with normoglycemia), "pre-diabetes" (hyperinsulinemia with mildly elevated blood glucose), the "T2DM stage" (concomitant hyperinsulinemia and hyperglycemia), and the "pseudo-type 1 diabetes" stage (hyperinsulinemia accompanied by hyperglycemia and impaired pancreatic beta-cell function).

While this model illustrates the multi-stage progression and inherent heterogeneity of T2DM [8], it primarily focuses on classification for diagnostic purposes. It fails to explore the underlying etiologies contributing to these three phenotypes, nor does it provide a comparative analysis regarding differences in pancreatic islet function, biochemical metabolic profiles, risks of complications, or therapeutic strategies among these subtypes.

Consequently, various T2DM classification methods have emerged, grounded in multidimensional data including genetics, metabolism, and clinical laboratory parameters. A landmark study published in Nature, titled "Genetic drivers of heterogeneity in type 2 diabetes pathophysiology," performed a large-scale meta-analysis of genome-wide association studies (GWAS) encompassing 2.5 million individuals of diverse ancestries. This study elucidated the etiological heterogeneity of T2DM from a genetic perspective [9]. By performing unsupervised clustering on 1,289 landmark single-nucleotide variants (SNVs), the researchers identified eight distinct subtypes: beta-cell function-increased, beta-cell function-decreased, residual glycemic, body fat, metabolic syndrome, obesity, and lipodystrophy clusters [9]. While this genomic approach has begun to unravel the etiological complexity underlying the onset and progression of T2DM, its clinical utility remains severely constrained. Genetic testing is not universally accessible across all healthcare facilities and involves significant ethical concerns regarding genomic security. As a result, genotype-based subtyping is currently more prevalent in scientific research than in routine clinical practice.

Another pivotal study, "Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables," conducted a cluster analysis on a cohort of newly diagnosed diabetes patients in Scania, Sweden. Based on six variables—glutamate decarboxylase antibodies (GADA), age at diagnosis, Body Mass Index (BMI), HbA1c, pancreatic beta-cell function, and insulin resistance—the study identified five distinct clusters: Severe Autoimmune Diabetes (SAID), Severe Insulin-Deficient Diabetes (SIDD), Severe Insulin-Resistant Diabetes (SIRD), Mild Obesity-Related Diabetes (MOD), and Mild Age-Related Diabetes (MARD). Among these, individuals in the SAID and SIDD clusters exhibited higher HbA1c levels and a greater predisposition to ketoacidosis. Notably, the SIRD cluster was characterized by severe insulin resistance, high BMI, and the strongest association with metabolic dysfunction-associated steatotic liver disease(MASLD); patients in this cluster also derived the most significant benefit from metformin therapy. By utilizing objective statistical analysis of clinical variables, this study categorized diabetes into five subtypes, reflecting the inherent heterogeneity in the onset, progression, and complications across different populations [10]. However, this research was not exclusively focused on T2DM.

Furthermore, the extensive range of required measurements and laboratory parameters complicates the rapid and simple subtyping of patients, thereby limiting its widespread clinical implementation.

To address the metabolic heterogeneity of T2DM and its prodromal stages, the study "Predicting Type 2 Diabetes Metabolic Phenotypes Using Continuous Glucose Monitoring and a Machine Learning Framework" employed a novel approach. The authors first constructed glucose curves using 16 time points from a standardized oral glucose tolerance test (OGTT) in a discovery cohort. Simultaneously, they utilized "gold-standard" metabolic tests to quantify physiological defects in each participant, categorizing them into four distinct metabolic subtypes: muscle insulin resistance, beta-cell dysfunction, impaired incretin effect, and hepatic insulin resistance. After developing a machine learning model based on the discovery cohort, its accuracy was confirmed using a validation cohort. Ultimately, data from a home-based Continuous Glucose Monitoring (CGM) cohort were integrated into the model, demonstrating that home CGM can effectively classify metabolic subtypes in patients with pre-diabetes and T2DM, as well as predict muscle insulin resistance and beta-cell function[11]. However, the study population was limited to individuals with pre-diabetes or mild T2DM, excluding those with more advanced disease. Furthermore, while home CGM offers continuous and intelligent monitoring, it possesses inherent limitations, including physiological time lags, reduced accuracy at glucose extremes, and the ongoing requirement for finger-stick blood glucose calibration [12].

While numerous T2DM classification systems have been proposed, each possesses distinct strengths and weaknesses, and they all face significant constraints that hinder their large-scale implementation. Consequently, it remains imperative to explore a more accessible and universally applicable classification framework tailored to the broader T2DM population, which can effectively guide both preventive and therapeutic strategies.

Impact of Adiposity, Fat Distribution, and Skeletal Muscle on Diabetes

Effects of Adipose Tissue on Islet Function and Glucose Metabolism

Adipose tissue produces non-esterified fatty acids (NEFA; also referred to as free fatty acids, FFA), glycerol, leptin, adiponectin, and pro-inflammatory cytokines[13, 14]. Elevated NEFA levels are observed in obesity and type 2 diabetes, and are considered to be closely linked to insulin resistance[15]. A study titled "Partial inhibition of adipose tissue lipolysis improves glucose metabolism and insulin sensitivity without alteration of fat mass" explored the role of hormone-sensitive lipase (HSL) expression in regulating lipolysis. By comparing wild-type mice with HSL-haploinsufficient mice, the researchers found that HSL haploinsufficiency resulted in reduced lipolysis in white adipose tissue and a slower turnover of NEFA. Crucially, the study demonstrated increased glucose uptake in the skeletal muscle, liver, and white adipose tissue of HSL-haploinsufficient mice, without significant alterations in insulin secretion. These findings suggest that lowering NEFA levels can effectively improve insulin resistance [16].

NEFA exerts its effects on glucose metabolism through a multitude of mechanisms. Primarily, NEFAs act as extracellular ligands that activate G protein-coupled receptors (GPCRs) on the plasma membrane, specifically binding to and signaling through GPR40, GPR120, GPR84, GPR41, and GPR43 [17]. Binding of NEFAs to GPR40 triggers Gαq/11 signaling, which elevates intracellular calcium concentrations and activates phospholipases to generate diacylglycerol (DAG), thereby augmenting insulin secretion [13]. Furthermore, GPR40 is expressed in enteroendocrine cells (such as L-cells and K-cells); its activation stimulates the secretion of incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which subsequently act on pancreatic beta-cells [18]. Similarly, GPR120 promotes insulin release by increasing GLP-1 secretion from enteroendocrine cells and mediates anti-apoptotic effects in beta-cells via the activation of extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) pathways [17].

However, chronic exposure to elevated NEFA levels results in lipotoxicity and beta-cell dysfunction. An excess of long-chain saturated free fatty acids drives the de novo synthesis of sphingolipids by providing increased substrates for key enzymes, namely serine palmitoyltransferase (SPT) and ceramide synthase (CerS), ultimately leading to the accumulation of ceramide [17]. Ceramide, in turn, induces beta-cell apop-

tosis by forming protein-permeable channels in the mitochondrial membrane [19], inactivating Akt, or enhancing the generation of reactive oxygen species (ROS) to promote cytochrome c release [17]. Additionally, a study titled "Initiation and execution of lipotoxic ER stress in pancreatic beta-cells" demonstrated that exposure of INS-1E cells, FACS-purified primary rat beta-cells, and human islet cells to palmitate (a saturated fatty acid)—but not to non-metabolizable methyl-FFA analogs used as controls—triggered endoplasmic reticulum (ER) stress, ultimately culminating in cell apoptosis[20].

FFAs also contribute to the development of adipose tissue inflammation. The study "TLR4 links innate immunity and fatty acid-induced insulin resistance" demonstrated that FFAs activate NF-κB reporter genes and cytokine expression in macrophages via TLR4 signaling. Using a 200 μM oleate/palmitate mixture to stimulate TLR4 (with 100 ng/ml LPS as a positive control), the researchers proved that FFAs can mimic LPS in activating NF-κB signaling. Furthermore, treatment of macrophages from both wild-type and TLR4-deficient mice revealed that FFAs induced TNF-α and IL-6 mRNA expression only in wild-type cells, indicating that FFAs leverage TLR4 signaling to elicit inflammatory responses in macrophages [21]. Beyond these mechanisms, FFAs can activate the NLRP3-PYCARD inflammasome, leading to the production of caspase-1, IL-1β, and IL-18. Both TNF-α and IL-1β significantly enhance the serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1) at Ser307, which inhibits insulin-induced PI3K-Akt activation and ultimately results in insulin resistance [22].

In addition to the effects of FFAs, the expansion of adipose tissue leads to relative hypoperfusion or increased oxygen consumption, resulting in tissue hypoxia. This cellular hypoxia may, in turn, trigger inflammation by inducing the HIF-1 genetic program [23]. Chemokines produced during adipose inflammation drive the infiltration of pro-inflammatory macrophages, predominantly of the M1 (classically activated) phenotype [23]. An increase in macrophage density is a hallmark of obesity-related adipose tissue inflammation. In the state of obesity, adipose hypertrophy, hyperplasia, and the loss of tissue homeostasis shift adipokine production from adiponectin to leptin and Monocyte Chemoattractant Protein-1 (MCP-1). This triggers a Type 1 (IFN-γ-based) inflammatory response, which eventually drives the polarization of adipose tissue macrophages from an anti-inflammatory M2-like state to a pro-inflammatory M1-like phenotype [24], generating a cascade of pro-inflammatory cytokines and establishing a vicious cycle.

These pro-inflammatory cytokines further exacerbate insulin resistance, elevate blood glucose, and can even impair pancreatic beta-cell function. TNF-α inhibits insulin-stimulated glucose uptake in muscle and adipose tissues by decreasing GLUT4 mRNA transcription or shortening its half-life [25-27]. It also activates the JNK pathway, leading to the serine phosphorylation of IRS-1 and the subsequent inhibition of insulin-induced tyrosine phosphorylation of IRS-1 and IRS-2 [28]. Conversely, IL-6 exhibits complex roles; it can act directly on beta-cells to enhance glucose-stimulated insulin secretion or stimulate fatty acid oxidation and glucose uptake. During exercise, muscle-derived IL-6 increases naturally and is associated with improved insulin sensitivity and nutrient availability [29]. IL-6 also regulates beta-cell autophagy via the activation of AMPK, inhibition of mTORC1, and activation of Akt, thereby protecting beta-cells from cytokine-induced apoptosis [30]. Nevertheless, clinical data show that IL-6 levels correlate positively with fasting blood glucose, HbA1c, and triglycerides, suggesting its involvement in the pathogenesis and progression of diabetes [31].

Beyond the aforementioned mechanisms, adipose tissue also modulates glucose and lipid metabolism through the secretion of a wide array of adipokines. Adipose tissue produces adiponectin, which acts on AdipoR1 and AdipoR2 receptors to activate the AMPK signaling pathway. This activation stimulates the translocation of GLUT4 to the plasma membrane, thereby increasing glucose transport [32, 33]. Conversely, leptin is primarily synthesized by adipose tissue and acts on the arcuate nucleus of the hypothalamus. It exerts its anorexigenic (appetite-suppressing) effects by inhibiting agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons while stimulating pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons. Furthermore, leptin can inhibit insulin secretion from pancreatic beta-cells; however, circulating leptin levels correlate positively with insulin resistance. The emergence of leptin re-

sistance is typically concomitant with the development of insulin resistance [34].

Roles of Skeletal Muscle in Islet Function and Glycemic Regulation

Skeletal muscle significantly influences glucose metabolism through the direct uptake of circulating glucose. It facilitates glucose absorption by triggering GLUT4 translocation to the plasma membrane via both insulin-mediated and non-insulin-mediated signaling pathways. In the insulin-mediated pathway, insulin acts on skeletal muscle PI3K to activate Akt and Rac1, ultimately driving GLUT4 translocation. Insulin resistance occurs when there is a reduction in IRS-1 tyrosine phosphorylation or protein abundance, alongside impaired PI3K activity, defective Rac1 activation, or dysfunctional Rac1-mediated actin remodeling. Conversely, the non-insulin-mediated mechanism is triggered by muscle contraction, which elevates ADP and AMP levels to activate the AMPK signaling pathway. This promotes GLUT4 translocation and glucose uptake independently of insulin. When skeletal muscle receives adequate nutrient-rich blood perfusion and maintains sufficient membrane permeability to glucose—coupled with the ability to sustain a diffusion gradient through storage and metabolism—substantial amounts of glucose can be cleared, thereby maintaining systemic carbohydrate homeostasis [35-37].

Furthermore, skeletal muscle secretes myokines that modulate glucose metabolism, insulin sensitivity, and pancreatic function [38]. Irisin, for instance, activates browning-related genes via the ERK-p38 MAPK pathway to induce the browning of white adipose tissue and upregulate GLUT4 expression in mature adipocytes. It also activates AMPK to enhance GLUT4 translocation in muscle tissue, significantly increasing the uptake of glucose and fatty acids [39]. Moreover, irisin promotes beta-cell proliferation through the ERK and p38 MAPK pathways [40]. Notably, hyperglycemia in diabetic patients may further stimulate irisin secretion from muscle tissue [41]. Additionally, muscle contraction or depleted glycogen levels trigger the secretion of IL-6, elevating its circulating concentrations. This muscle-derived IL-6 enhances peripheral insulin sensitivity and increases both basal and insulin-stimulated glucose uptake; it also counteracts insulin resistance by inhibiting the production of TNF-α [42]. Beyond these, skeletal muscle produces other myokines, including fibroblast growth factor 21 (FGF21), secreted protein acidic and rich in cysteine (SPARC), β-aminoisobutyric acid (BAIBA), brain-derived neurotrophic factor (BDNF), musclin, and myostatin, all of which play roles in regulating glucose metabolism [43].

Influence of Regional Fat and Muscle Distribution on Islet Function and Metabolism

In summary, adipose and muscle tissues influence pancreatic function, insulin sensitivity, and glucose metabolism through diverse pathways. Furthermore, the regional distribution of these tissues plays a critical role in metabolic regulation [44].

Based on distinct distributional characteristics, obesity can be categorized into abdominal (android) obesity, gluteofemoral (gynoid) obesity, and ectopic fat deposition. Abdominal obesity is significantly and positively correlated with insulin resistance, T2DM, and cardiovascular disease [45, 46]. Conversely, gluteofemoral fat is inversely associated with these metabolic risks [47, 48]. This protective effect may stem from the fact that gluteofemoral fat is positively correlated with adiponectin and leptin levels, whereas abdominal fat exhibits lower adiponectin secretion and is often accompanied by leptin resistance [49, 50]. Lipoprotein lipase (LPL), a key enzyme secreted by adipose or muscle tissues to hydrolyze triglycerides in VLDL and chylomicrons, also influences glucose metabolism; increased LPL expression correlates positively with glucose and insulin tolerance [51]. Notably, LPL activity is higher in gluteofemoral adipose tissue than in abdominal fat, providing it with a superior capacity for postprandial fatty acid entrapment [52].

Extensive clinical evidence confirms a potent positive correlation between visceral adipose tissue (VAT) and insulin resistance. VAT also impacts both basal and stimulated insulin secretion. Reductions in VAT through diet or exercise significantly alleviate insulin resistance [53-56]. This may be attributed to the "portal theory," where free fatty acids (FFAs) from VAT drain directly into the liver via the portal vein, stimulating hepatic gluconeogenesis and reducing hepatic insulin extraction [57].

Ectopic fat deposition further impairs systemic metabolism. Intermuscular Adipose Tissue (IMAT), a

unique ectopic depot with a transcriptome distinct from subcutaneous or visceral fat, releases pro-inflammatory cytokines and adipokines that disrupt glucose and lipid metabolism. IMAT promotes intramyocellular lipid accumulation by increasing interstitial FFA concentrations, interferes with mitochondrial function, and induces 1,2-diacylglycerol accumulation, thereby exacerbating skeletal muscle insulin resistance [58].

Similarly, Non-Alcoholic Fatty Pancreas Disease (NAFPD), characterized by pancreatic steatosis excluding infectious or genetic causes, results from either adipocyte replacement after cell necrosis or ectopic infiltration. Obesity, leptin deficiency, and aging are closely linked to NAFPD. Pancreatic lipotoxicity and infiltration trigger beta-cell dysfunction and necrosis, serving as major risk factors for diabetes and metabolic syndrome [59]. Furthermore, NAFLD involves ectopic lipid accumulation in the liver, which inhibits insulin signaling, reduces glycogen synthesis, and increases gluconeogenesis through pathways involving adipokines, inflammation, and endoplasmic reticulum (ER) stress [60].

Skeletal muscle mass in different regions also profoundly affects glucose metabolism. A cross-sectional study by Tanaka et al. [61] demonstrated that low skeletal muscle density and mass are significantly associated with metabolic syndrome. Another study involving 272 non-diabetic elderly individuals found that lower limb and appendicular muscle mass are linked to insulin resistance risk [62]. In diabetic patients, height-adjusted lower limb muscle mass is particularly closely correlated with insulin resistance.

Beyond individual tissue content, the ratio of muscle to fat is of paramount importance. Sarcopenia is characterized by a progressive loss of muscle mass due to aging (primary) or pathological states such as cachexia and organ failure (secondary). When sarcopenia co-occurs with increased adiposity, it is termed Sarcopenic Obesity (SO)[63]. Insulin resistance disrupts protein metabolism, leading to muscle loss, while hyperglycemia further accelerates muscle atrophy via the ubiquitin-proteasome proteolytic pathway [63, 64]. Compared to non-sarcopenic obese individuals, those with SO face significantly higher risks of hyperglycemia, hypertension, dyslipidemia, and insulin resistance [64]. Abnormal levels of growth hormone, testosterone, and estradiol in SO patients activate signaling pathways such as IKK/NF-κB, JNK, PKC, and JAK/STAT in skeletal muscle, ultimately driving insulin resistance [65]. Additionally, reduced mitochondrial number and impaired function in sarcopenic muscle further exacerbate these metabolic disturbances [64].

Subtyping Type 2 Diabetes Based on Body Fat Distribution and Composition

In summary, T2DM patients with varying skeletal muscle mass, fat mass, and distribution patterns exhibit distinct clinical profiles in terms of glucose metabolism, pancreatic function, and insulin resistance. These phenotypic differences translate into disparate risks for cardiovascular events, diabetic kidney disease (DKD), MASLD, and peripheral nerve damage [44]. Consequently, numerous studies have attempted to classify T2DM patients based on adipose and muscle content, revealing that these subtypes possess unique metabolic signatures and complication risks.

A retrospective clinical study involving 240 subjects (120 with T2DM and 120 non-diabetic controls) utilized conventional CT scans at the L3 vertebral level to assess abdominal, pelvic, and renal regions. Using specialized fat-analysis software to measure visceral and subcutaneous fat volumes, the study demonstrated that both visceral and subcutaneous fat were significantly higher in T2DM patients compared to non-diabetic individuals, highlighting substantial differences in total fat content and distribution patterns [66].

Bouchi et al. [67] further stratified 148 T2DM patients into four groups based on CT-derived visceral fat area (VFA) and subcutaneous fat area (SFA): SFA < 100 cm² and VFA < 100 cm² (S-/V-); SFA ≥ 100 cm² and VFA < 100 cm² (S+/V-); SFA ≥ 100 cm² and VFA ≥ 100 cm² (S+/V+); and SFA < 100 cm² and VFA ≥ 100 cm² (S-/V+). By evaluating atherosclerosis through carotid intima-media thickness (CIMT) measurements, they found that the S-/V+ phenotype was positively correlated with atherosclerosis, while the S+/V+ phenotype showed a negative correlation. Although this study accurately quantified fat distribution using CT-based subtyping, it focused exclusively on atherosclerotic risk without exploring potential differences in glucose and lipid metabolism across the groups. Furthermore, the confounding influence

of skeletal muscle mass and distribution—which also impacts glucose metabolism and insulin resistance—was not addressed.

In another study, "Sarcopenic obesity is associated with macroalbuminuria in patients with type 2 diabetes: a cross-sectional study," 206 male and 163 female T2DM patients underwent multi-frequency bioelectrical impedance analysis (BIA). The researchers defined sarcopenia as low skeletal muscle mass index (SMI < 7.0 kg/m² for men, < 5.7 kg/m² for women) combined with low grip strength (< 28 kg for men, < 18 kg for women), while obesity was defined by high body fat percentage (> 30% for men, > 35% for women). Patients were categorized into four phenotypes: non-sarcopenic non-obese, sarcopenic only, obese only, and sarcopenic obese. Renal function was assessed via HbA1c, serum creatinine, uric acid, eGFR, and urinary albumin excretion rate (UAER). The results indicated that sarcopenic obesity (SO) was significantly associated with more advanced stages of diabetic kidney disease and macroalbuminuria, even after adjusting for covariates such as age and sex [68]. While BIA-based body composition analysis is radiation-free and highly applicable in clinical settings, this study was limited to renal complications and did not investigate lipid metabolism or insulin resistance. Moreover, as the definitions of sarcopenia and SO remain a subject of debate [65], the diagnostic cut-off points used in this study carry a degree of subjectivity.

To conclude, T2DM patients can be effectively subtyped based on adipose and muscle content and distribution, with each subtype exhibiting unique metabolic characteristics and complication risks. However, a standardized, universally applicable classification system based on body composition remains lacking, which is essential for guiding precision medicine and individualized therapeutic strategies in T2DM.

Conclusion

In an era of escalating diabetes prevalence, the shift toward precision and individualized management has become the definitive trend in clinical endocrinology. Adipose and skeletal muscle tissues exert profound influence on glucose homeostasis and pancreatic function through diverse pathways, including the secretion of specific adipokines and myokines. Crucially, the quantitative and distributional heterogeneity of these tissues serves as a pivotal determinant of metabolic health. Emerging clinical evidence suggests that characterizing the content and distribution of fat and muscle can effectively predict pancreatic beta-cell function, the degree of insulin resistance, and the risk of chronic complications in patients with type 2 diabetes (T2DM). By quantifying these parameters, T2DM patients can be broadly categorized into four distinct metabolic phenotypes(figure1): (1) Normal Composition :optimal muscle and fat balance; (2) Sarcopenic :normal fat mass with reduced muscle mass; (3) Simple obesity :increased adipose tissue with normal muscle mass; (4) Sarcopenic obesity :concomitant reduction in muscle mass and increase in adiposity. This classification framework offers a potent tool for predicting the unique glucose metabolic profiles and complication trajectories associated with each subtype.

To date, various modalities are available for assessing body composition. While traditional anthropometric indices such as waist circumference and waist-to-hip ratio are easily accessible, they fail to provide a direct and nuanced evaluation of tissue-specific quality and distribution. In contrast, advanced imaging techniques offer superior accuracy. Computed Tomography (CT) remains the "gold standard" for adipose quantification; however, its high cost and significant ionizing radiation limit its utility in routine screening. Dual-energy X-ray absorptiometry (DXA), which utilizes two distinct X-ray energy levels to differentiate tissues based on attenuation gradients, allows for the precise calculation of bone mineral content (BMC), fat mass (FM), and lean soft tissue mass (LST). DXA further excels by providing detailed regional analysis of body fat distribution [69]. Bioelectrical impedance analysis (BIA) estimates lean mass and fat mass based on conductivity differences between water-rich lean tissues and anhydrous adipose tissue [70]. While BIA is portable and radiation-free, it is susceptible to fluctuations in hydration status, often overestimating body fat percentage in lean individuals while underestimating it in obese subjects [71]. Given its superior accuracy compared to BIA and its lower cost and radiation compared to CT, DXA represents a highly viable and scalable tool for clinical implementation [72].

Looking forward, the integration of DXA-based precision phenotyping into the initial assessment of indi-

viduals with impaired glucose tolerance or newly diagnosed T2DM holds immense clinical promise. By identifying specific body composition phenotypes early, clinicians can predict metabolic risks and complication susceptibility with greater granularity. This approach will facilitate early targeted interventions and truly individualized therapeutic regimens, ultimately playing a critical role in preventing the onset and halting the progression of diabetes.

Declarations

Authors' Contributions

Made substantial contributions to the conception and design of the study, performed data analysis and interpretation, and drafted the manuscript: Xintong Zhang.

Performed data acquisition and literature search, as well as provided technical and material support: Rui Zhang.

Provided administrative, technical, and material support, and performed critical revision of the manuscript for important intellectual content: Tao Jiang.

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Conflicts of Interest

All authors declared that there are no conflicts of interest.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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