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Review Article

Type 2 Diabetes Mellitus: From Metabolic Dysfunction Syndrome to Precision Prevention and Targeted Therapy

Putri Karenina Amalia Wulandari[1*], Dhiny Sylvana[1], Suandy[2,3]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Prima Indonesia, Medan, Indonesia
[2]Department of Clinical Medicine, Universitas Prima Indonesia
[3]Center of Excellence for Phyto Degenerative & Lifestyle Medicine, Universitas Prima Indonesia

*Corresponding author: putrikarenina19@gmail.com

Abstract

Type 2 diabetes mellitus (T2DM) remains a prevalent metabolic disorder worldwide, continuously imposing a substantial clinical and socioeconomic burden. Traditionally viewed as a glucose-centered disease characterized by hyperglycemia driven by insulin resistance and pancreatic beta-cell dysfunction, recent evidence clearly indicates that hyperglycemia is merely a downstream manifestation of broader metabolic abnormalities. Advances in molecular biology, immunometabolism, and systems biology have facilitated the emergence of Metabolic Dysfunction Syndrome (MDS) as a comprehensive framework for understanding T2DM pathogenesis. This review summarizes the interconnected roles of insulin resistance, adipose tissue dysfunction, ectopic lipid accumulation, chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, progressive beta-cell failure, and inter-organ crosstalk in disease progression. Furthermore, we extensively discuss the vital clinical implications of this paradigm shift, highlighting the critical importance of early risk stratification, prescreening, timely diagnosis, and personalized therapeutic algorithms extending beyond mere glycemic control. Emerging pharmacological therapies with cardiometabolic and reno-protective benefits, combined with holistic lifestyle interventions, firmly support a vital transition from reactive glucose-lowering strategies to proactive disease-modifying approaches targeting underlying metabolic dysfunction. Ultimately, adopting the MDS framework provides a highly integrated understanding of T2DM, directly offering unprecedented opportunities for precision prevention, individualized treatment, and improved long-term clinical outcomes globally for all affected patients.

Keywords: Type 2 diabetes mellitus, Metabolic dysfunction syndrome, Chronic inflammation, Inter-organ crosstalk, Precision medicine.

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1 Introduction

Type 2 diabetes mellitus (T2DM) has emerged as one of the most pressing global public health challenges of the twenty-first century, with its prevalence increasing at an alarming rate across both developed and developing countries (1-2). Driven by rapid urbanization, population aging, sedentary lifestyles, unhealthy dietary patterns, and the escalating prevalence of obesity, T2DM now affects hundreds of millions of individuals worldwide and is projected to continue rising over the coming decades (3). Beyond its high prevalence, T2DM represents a major contributor to premature mortality and disability due to its association with debilitating microvascular and macrovascular complications, including cardiovascular disease, chronic kidney disease, diabetic retinopathy, peripheral neuropathy, and metabolic dysfunction-associated steatosis liver disease (MASLD) (2,4,5). Consequently, the disease imposes an enormous burden not only on affected individuals but also on healthcare systems and national economies, resulting in substantial direct medical expenditures and indirect costs arising from reduced productivity, disability, and diminished quality of life (2,6).

Conventionally, T2DM has been conceptualized as a glucocentric disorder characterized primarily by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both (1,7). This perspective has shaped clinical management for decades, with therapeutic strategies predominantly focused on lowering blood glucose levels to prevent diabetes-related complications (4,6,7). Although intensive glycemic control has undoubtedly improved clinical outcomes, accumulating evidence indicates that normalization of blood glucose alone is insufficient to halt disease progression or fully prevent long-term cardiovascular, renal, and metabolic complications (5,8). Many patients continue to experience progressive β-cell dysfunction, worsening insulin resistance, and persistent systemic metabolic abnormalities despite achieving recommended glycemic targets (8). These observations suggest that hyperglycemia represents a downstream clinical manifestation rather than the primary driver of disease pathogenesis, highlighting the limitations of the traditional glucocentric model (9).

Recent advances in metabolic research have therefore prompted a paradigm shift in our understanding of T2DM, recognizing it as a manifestation of the broader entity known as Metabolic Dysfunction Syndrome (MDS) (9,10). Rather than being solely a disorder of glucose metabolism, T2DM is increasingly viewed as a complex, multisystem disease resulting from chronic metabolic dysfunction involving multiple organs and interconnected biological pathways (2,8,11). This emerging framework integrates systemic insulin resistance, adipose tissue dysfunction, ectopic lipid deposition, chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, impaired inter-organ communication, and progressive pancreatic β-cell failure into a unified pathogenic model (10,12). Importantly, these metabolic disturbances often develop years before the onset of overt hyperglycemia, reflecting a prolonged period of subclinical disease progression (12). The intricate crosstalk among adipose tissue, liver, skeletal muscle, pancreas, gut, kidney, immune system, and central nervous system further underscores the systemic nature of T2DM and provides a more comprehensive explanation for its heterogeneous clinical manifestations and associated complications (10,13).

The recognition of T2DM as a systemic metabolic disorder has been accompanied by remarkable advances in molecular biology, immunometabolism, multi-omics technologies, and precision medicine, substantially expanding our understanding of the mechanisms underlying disease initiation and progression (7,14). Emerging evidence highlights the pivotal roles of chronic inflammation, immune cell activation, mitochondrial dysfunction, gut microbiota dysbiosis, and metabolic signaling networks in shaping disease susceptibility and therapeutic responses (10,13,15). Moreover, the development of novel therapeutic agents that confer cardiovascular and renal protection beyond glycemic control further supports a transition from glucose-centered treatment toward comprehensive metabolic risk modification and disease prevention (15,16). Collectively, this review aims to provide a comprehensive overview of the current understanding of T2DM by integrating recent advances in its epidemiology, molecular pathogenesis, and therapeutic strategies within the framework of MDS. Particular emphasis is placed on the interconnected mechanisms linking insulin resistance, β-cell dysfunction, chronic inflammation,

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mitochondrial impairment, and inter-organ metabolic crosstalk. Furthermore, this review discusses contemporary preventive approaches, established pharmacological interventions, and emerging disease-modifying therapies, including precision medicine and regenerative strategies, with the goal of providing a holistic perspective that may facilitate the development of more effective strategies for preventing disease progression and improving long-term clinical outcomes.

2 Discussion

2.1 Metabolic Dysfunction Syndrome: The Foundation of T2DM Development

Type 2 diabetes mellitus (T2DM) is increasingly recognized as a manifestation of MDS rather than a disease driven solely by hyperglycemia (20). MDS represents a systemic metabolic disorder characterized by impaired energy homeostasis resulting from the complex interplay of genetic predisposition, excessive caloric intake, sedentary lifestyle, and aging (1,9). These factors collectively disrupt metabolic regulation long before the onset of overt diabetes, giving rise to interconnected abnormalities such as insulin resistance, adipose tissue dysfunction, ectopic lipid accumulation, oxidative stress, chronic low-grade inflammation, and progressive β-cell impairment (21). This paradigm shift highlights that hyperglycemia is a downstream consequence of widespread metabolic dysfunction rather than the initiating pathological event.

Obesity, particularly visceral obesity, is a major contributor to MDS through its detrimental effects on adipose tissue function (21,22). As adipocytes become hypertrophic and exceed their lipid storage capacity, excess fatty acids are redistributed to non-adipose organs, including the liver, skeletal muscle, pancreas, and kidneys, leading to ectopic fat accumulation and lipotoxicity (22). Within these tissues, excess fatty acids are converted into bioactive lipotoxic intermediates, particularly ceramides and diacylglycerols (DAGs), which disrupt insulin signaling by activating protein kinase C (PKC) isoforms and other stress-responsive kinases. These kinases promote inhibitory serine phosphorylation of insulin receptor substrate (IRS)-1, thereby impairing IRS-mediated activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway. Consequently, insulin-stimulated GLUT4 translocation and cellular glucose uptake are diminished, resulting in systemic insulin resistance (22,23). Concurrently, chronic nutrient excess induces metabolic stress by promoting mitochondrial dysfunction, endoplasmic reticulum stress, and excessive reactive oxygen species production (23). These disturbances further activate inflammatory signaling pathways, including NF-κB and JNK, exacerbating insulin resistance and β-cell dysfunction and establishing a self-perpetuating cycle of metabolic dysregulation that drives the progression toward T2DM (23).

2.2 Insulin Resistance: The Central Driver of Hyperglycemia

Insulin resistance is considered the earliest and most fundamental metabolic abnormality in T2DM, preceding clinical diagnosis by several years (19,23). It is characterized by a diminished biological response of insulin-sensitive tissues—including the liver, skeletal muscle, and adipose tissue—to circulating insulin, resulting in impaired glucose uptake and utilization despite normal or elevated insulin concentrations (6,23). Initially, pancreatic β-cells compensate by increasing insulin secretion to maintain normoglycemia; however, prolonged insulin resistance progressively overwhelms this compensatory capacity, ultimately leading to chronic hyperglycemia (14).

At the molecular level, insulin resistance arises from disruptions in insulin signaling pathways, particularly the insulin receptor substrate (IRS)/phosphoinositide 3-kinase (PI3K)/Akt cascade, which is essential for glucose transport and metabolic regulation (20,21). Impaired signaling reduces GLUT4 translocation to the plasma membrane in skeletal muscle and adipose tissue, thereby limiting glucose uptake, while hepatic insulin resistance promotes excessive gluconeogenesis and glucose output (24). These abnormalities are further exacerbated by chronic inflammation, oxidative stress, and lipid accumulation, which activate stress-responsive kinases and inflammatory mediators that interfere with insulin signaling and perpetuate metabolic dysfunction (2, 25).

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2.3 Progressive β-cell Dysfunction

The progressive decline in pancreatic β-cell function represents a defining feature of T2DM and ultimately determines the transition from compensated insulin resistance to overt diabetes (7,12). During the early stages of disease, β-cells respond to increasing insulin demand through adaptive mechanisms such as enhanced insulin synthesis, β-cell hypertrophy, and hyperinsulinemia (12,22). However, persistent metabolic stress gradually exhausts these compensatory responses, leading to impaired glucose-stimulated insulin secretion and a progressive reduction in functional β-cell mass (22). Multiple mechanisms contribute to β-cell deterioration, including chronic exposure to hyperglycemia (gluco-toxicity), elevated circulating free fatty acids (lipo-toxicity), oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction (25). Together, these insults impair insulin biosynthesis, disrupt cellular energy production, and activate apoptotic pathways, resulting in β-cell dedifferentiation and cell death (26). The combined effects of insulin resistance and progressive β-cell failure create a vicious cycle that accelerates disease progression and complicates long-term glycemic control (25,26).

2.4 Chronic Inflammation: Linking Obesity to Diabetes

Chronic low-grade inflammation is now recognized as a fundamental mechanism linking obesity to the onset and progression of T2DM (21,25). Unlike acute inflammation, which serves as a transient protective response, metabolic inflammation is persistent and arises from prolonged nutrient excess and adipose tissue dysfunction (26,27). During obesity, adipocytes undergo hypertrophy, leading to local hypoxia, extracellular matrix remodeling, and increased infiltration of immune cells, particularly macrophages (22,26). Consequently, adipose tissue shifts from an anti-inflammatory endocrine organ to a major source of pro-inflammatory mediators that disrupt systemic metabolic homeostasis (21). This inflammatory microenvironment not only impairs insulin sensitivity but also contributes to progressive pancreatic β-cell dysfunction, establishing inflammation as a central driver rather than merely a consequence of metabolic disease (1,25) (Figure 1).

Among the inflammatory mediators implicated in T2DM, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and the nuclear factor-kappa B (NF-κB) signaling pathway play pivotal roles in metabolic dysregulation (27,28). TNF-α interferes with insulin receptor substrate (IRS) signaling through inhibitory serine phosphorylation, thereby reducing downstream PI3K/Akt activation and impairing insulin-mediated glucose uptake (27,28). Similarly, chronically elevated IL-6 activates the JAK/STAT pathway and induces suppressor of cytokine signaling (SOCS) proteins, further attenuating insulin signaling and promoting hepatic gluconeogenesis (29,30). These cytokines, together with nutrient overload and oxidative stress, activate NF-κB, a master transcription factor that coordinates the expression of numerous pro-inflammatory genes, including TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) (30). Sustained NF-κB activation establishes a feed-forward inflammatory loop that perpetuates insulin resistance, oxidative stress, and β-cell dysfunction across multiple metabolic tissues (27).

Obesity-induced inflammation is further amplified by alterations in immune cell composition and adipokine secretion within adipose tissue (27,31). Lean adipose tissue is predominantly enriched with anti-inflammatory M2 macrophages that support insulin sensitivity, whereas obesity promotes polarization toward the pro-inflammatory M1 phenotype, resulting in increased production of TNF-α, IL-6, and other inflammatory mediators (29,32). Concurrently, the secretion of adipokines becomes dysregulated, characterized by reduced levels of the insulin-sensitizing adipokine adiponectin and increased concentrations of leptin, resistin, chemerin, and other pro-inflammatory factors (21,27). Reduced adiponectin signaling diminishes activation of AMP-activated protein kinase (AMPK) in skeletal muscle, leading to impaired fatty acid oxidation, reduced GLUT4 translocation, and decreased glucose uptake. The resulting accumulation of intracellular lipids further promotes insulin resistance by exacerbating defects in the IRS/PI3K/Akt signaling pathway. Meanwhile, elevated leptin and resistin contribute to persistent inflammatory signaling and metabolic dysfunction by enhancing the production

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of pro-inflammatory cytokines and further reducing insulin responsiveness (23,26). These coordinated alterations disrupt glucose and lipid metabolism, exacerbate insulin resistance, and promote chronic inflammation in the liver, skeletal muscle, and pancreatic islets (23,26). Collectively, chronic inflammation acts as a mechanistic bridge between obesity and T2DM, integrating immune activation with metabolic dysfunction and highlighting inflammatory pathways as promising targets for disease-modifying therapeutic strategies (25–27).

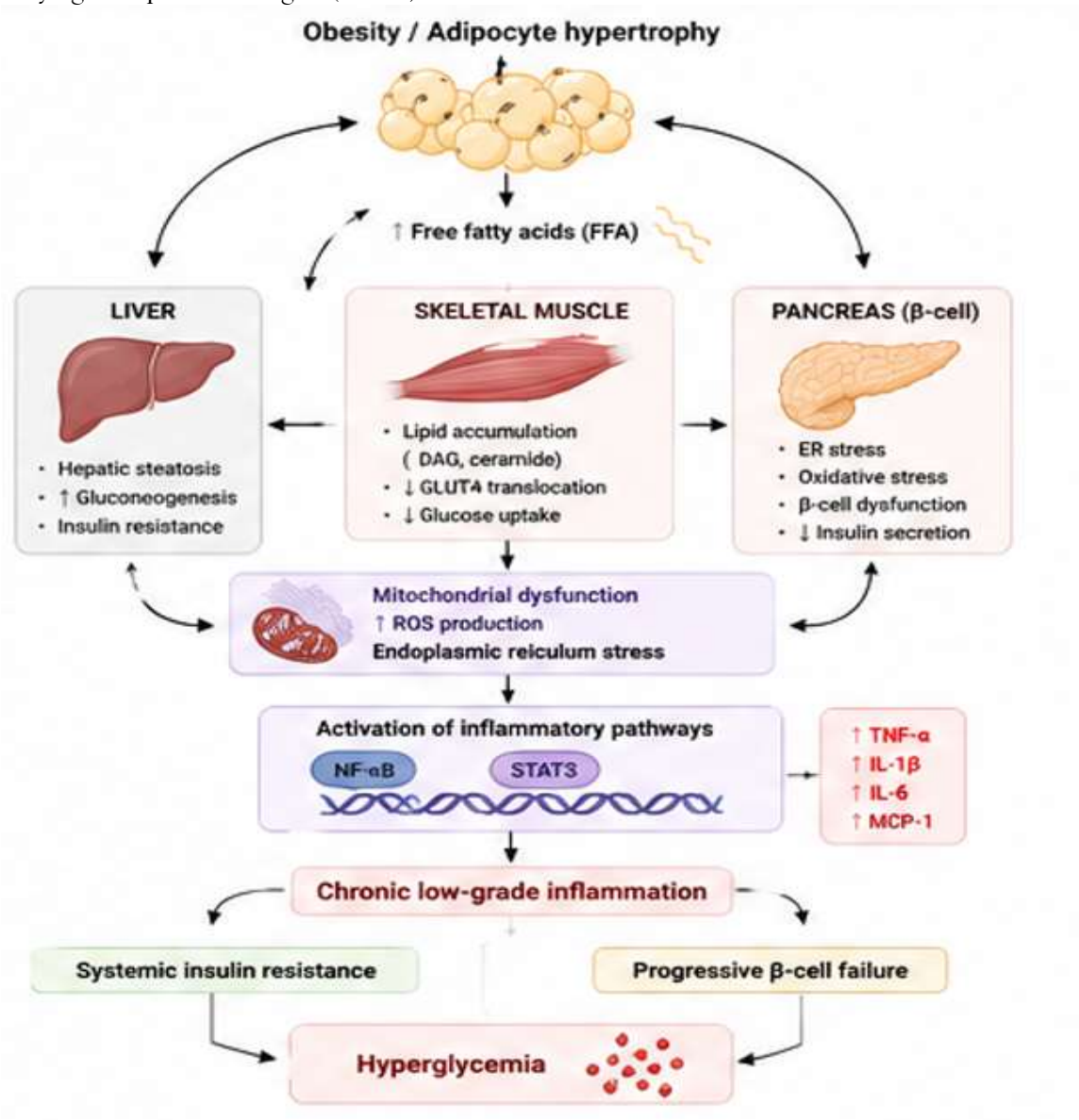

Figure 1. Integrated Molecular Mechanisms Underlying T2DM Development (adapted from [1,25])

2.5 Inter-Organ Crosstalk in T2DM

The pathogenesis of T2DM extends beyond isolated defects in individual organs and is increasingly understood as the result of disrupted communication among multiple metabolically active tissues (32,33). Glucose homeostasis depends on coordinated interactions between the liver, pancreas, skeletal muscle, adipose tissue, gastrointestinal tract, kidneys, and central nervous system through hormonal, neural, immune, and metabolic signaling networks (1,25) (Figure 2). Dysfunction in one organ can propagate metabolic abnormalities to others, creating an interconnected system that accelerates disease progression (25,26). Among these interactions, the liver–pancreas axis regulates the balance between hepatic glucose production and insulin secretion, while the gut–pancreas axis influences glucose metabolism through

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incretin hormones and gut microbiota-derived metabolites (33,34). The principal incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released from intestinal L cells and K cells, respectively, in response to nutrient ingestion. Upon binding to their G protein-coupled receptors on pancreatic β-cells, both hormones activate adenylyl cyclase, leading to increased cyclic AMP (cAMP) production and subsequent activation of protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac2). These signaling pathways enhance glucose-dependent insulin secretion by promoting insulin granule exocytosis and intracellular Ca^{2+} mobilization. GLP-1 signaling additionally suppresses glucagon secretion, delays gastric emptying, and promotes β-cell survival by reducing apoptosis and supporting β-cell function through activation of pro-survival pathways, including PI3K/Akt. In T2DM, the incretin effect is diminished, characterized by impaired responsiveness to GIP and reduced GLP-1 activity, contributing to defective insulin secretion and progressive β-cell dysfunction (33,34). Adipose tissue communicates with pancreatic β-cells through adipokines, free fatty acids, and inflammatory mediators, thereby modulating insulin secretion and sensitivity (34). Furthermore, the kidneys contribute to glucose homeostasis through glucose reabsorption and gluconeogenesis, whereas the hypothalamus integrates peripheral metabolic signals to regulate appetite, energy expenditure, and insulin responsiveness (25,26). Understanding these inter-organ networks provides a systems-level perspective of T2DM pathogenesis and provides a mechanistic basis for therapeutic strategies, such as GLP-1 receptor agonists, that restore incretin signaling while targeting multiple metabolic pathways simultaneously.

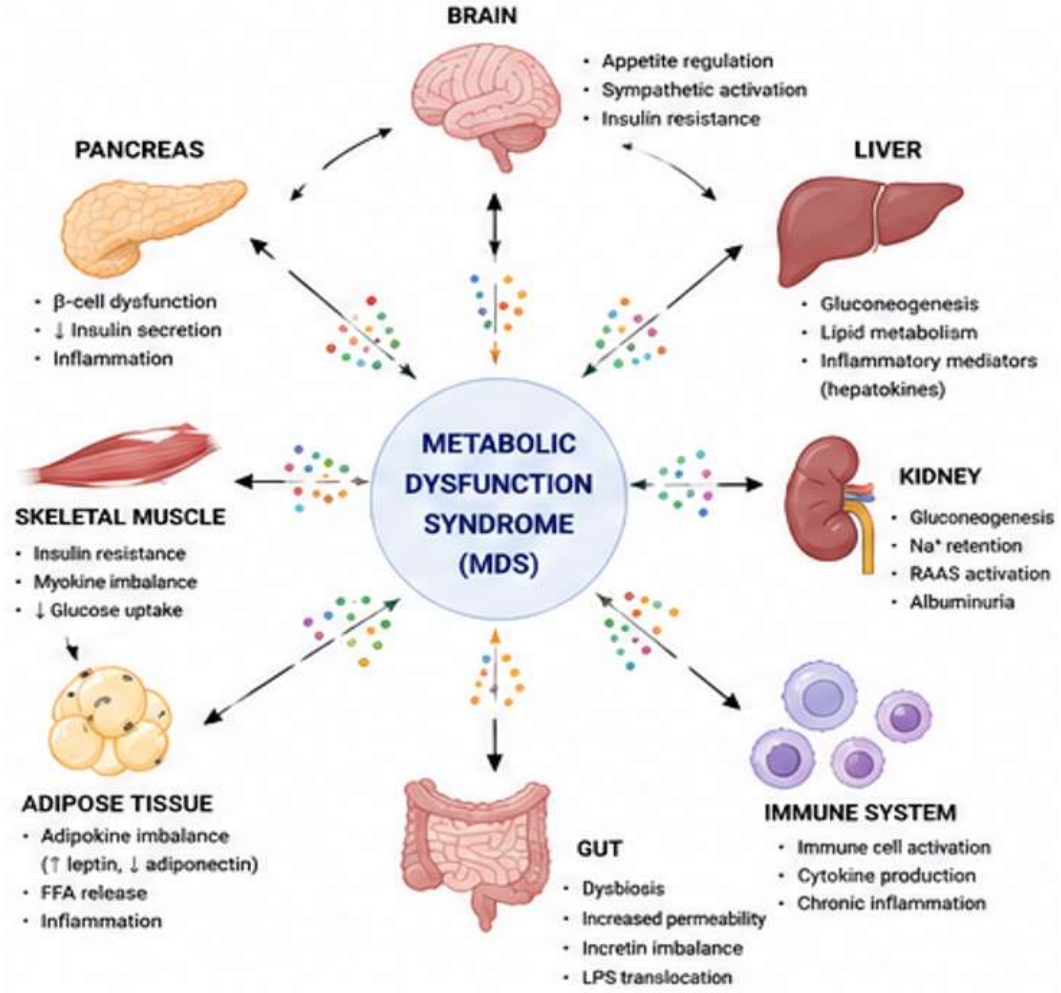

Figure 2. Metabolic Organ Crosstalk Driving Type 2 Diabetes Mellitus (adapted from [1,25])

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2.6 Limitations of the Traditional Glucocentric Concept

For decades, the pathogenesis and management of T2DM have been predominantly viewed through a glucocentric paradigm, in which chronic hyperglycemia is considered the defining feature and primary therapeutic target of the disease (5,12). Within this framework, T2DM has traditionally been attributed to impaired insulin secretion, insulin resistance, or a combination of both, with treatment strategies largely aimed at lowering blood glucose concentrations to reduce the risk of diabetes-related complications (20,29). This approach has driven the development of numerous glucose-lowering agents and has established HbA1c as the principal biomarker for disease monitoring and therapeutic success (31). Intensive glycemic control has undoubtedly reduced the incidence of microvascular complications, particularly diabetic retinopathy, nephropathy, and neuropathy, and remains an essential component of diabetes management (31).

Despite these therapeutic advances, accumulating clinical and experimental evidence suggests that a glucose-centered approach alone is insufficient to alter the natural history of T2DM (28). Many patients continue to experience progressive insulin resistance, declining β-cell function, and worsening metabolic abnormalities even after achieving recommended glycemic targets (34). Moreover, the residual risk of major cardiovascular events, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and other diabetes-related complications remains substantial, indicating that normalization of blood glucose does not fully address the underlying mechanisms driving disease progression (23,25). These observations highlight the limitations of focusing exclusively on glycemic control and suggest that hyperglycemia is primarily a downstream clinical manifestation of broader metabolic disturbances rather than the initiating pathological event (35). Consequently, contemporary research has shifted toward a more integrated understanding of T2DM as a systemic metabolic disorder involving chronic inflammation, mitochondrial dysfunction, ectopic lipid accumulation, oxidative stress, and dysregulated inter-organ communication (26). This paradigm shift has provided the rationale for developing therapeutic strategies that target upstream metabolic dysfunction in addition to achieving optimal glycemic control.

2.7 Emerging Concept: T2DM as a Manifestation of MDS

Recent studies have fundamentally reshaped the understanding of T2DM, shifting from the traditional glucocentric paradigm toward a broader systems biology perspective (35,36). Rather than considering hyperglycemia as the initiating pathological event, T2DM is increasingly recognized as a clinical manifestation of MDS, a complex disorder characterized by chronic disturbances in energy homeostasis and metabolic regulation (36). This emerging concept proposes that hyperglycemia represents the culmination of prolonged metabolic dysfunction rather than its primary cause. Consequently, T2DM should be viewed as the result of progressive pathological changes occurring across multiple organs and tissues, driven by interactions between genetic susceptibility, environmental exposures, and lifestyle-related factors (17,19,28).

MDS encompasses a network of interconnected metabolic abnormalities, including systemic insulin resistance, adipose tissue dysfunction, ectopic lipid accumulation, chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, impaired inter-organ communication, and progressive pancreatic β-cell failure (15,26,33). These pathological processes do not occur independently but instead reinforce one another through complex molecular and cellular signaling pathways (33). For example, adipose tissue dysfunction promotes excessive free fatty acid release and inflammatory cytokine production, which impair insulin signaling in the liver and skeletal muscle while simultaneously inducing oxidative and endoplasmic reticulum stress in pancreatic β-cells (26). Likewise, mitochondrial dysfunction exacerbates reactive oxygen species production, further amplifying inflammatory responses and metabolic impairment (26). Collectively, these mechanisms establish a self-perpetuating cycle of metabolic dysfunction that progressively deteriorates glucose homeostasis.

Importantly, many of these metabolic abnormalities develop years, or even decades, before the clinical diagnosis of T2DM (28,29). During this prolonged prediabetic phase, coordinated dysregulation

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among the liver, adipose tissue, skeletal muscle, pancreas, gastrointestinal tract, kidneys, immune system, and central nervous system gradually compromises insulin sensitivity and β-cell function (19,23,34). This intricate inter-organ communication is mediated through hormones, adipokines, cytokines, metabolites, extracellular vesicles, and neural signaling pathways that collectively regulate systemic metabolism (23,25,33). Recognizing T2DM within the framework of MDS therefore provides a more comprehensive understanding of disease initiation and progression, highlighting the importance of identifying upstream metabolic disturbances before irreversible β-cell damage occurs. This systems-based perspective also supports precision prevention and targeted therapy through comprehensive metabolic phenotyping that extends beyond glycemic indices. In addition to fasting plasma glucose and HbA1c, clinically relevant biomarkers—including high-sensitivity C-reactive protein (hs-CRP) as a marker of systemic inflammation, circulating adipokines such as adiponectin and leptin or the leptin-to-adiponectin ratio, lipid parameters including triglyceride-to-HDL cholesterol ratio, and emerging genetic or polygenic risk scores—may improve risk stratification, identify predominant pathophysiological mechanisms, and facilitate individualized therapeutic decision-making. Furthermore, advances in incretin-based therapies have expanded disease-modifying treatment strategies beyond conventional glucose lowering. Dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonists, such as tirzepatide, and investigational triple agonists targeting GLP-1, GIP, and glucagon receptors, such as retatrutide, simultaneously improve glycemic control, promote substantial weight reduction, enhance insulin sensitivity, and ameliorate multiple components of metabolic dysfunction. These multimodal agents exemplify the transition toward mechanism-based therapies that directly address the interconnected pathophysiology of MDS rather than hyperglycemia alone, supporting more personalized and disease-modifying approaches to T2DM management.

2.8 Conclusion Clinical Translation of the MDS Paradigm: From Early Detection to Personalized Management

The recognition of T2DM as a manifestation of MDS has fundamentally transformed the clinical approach to disease detection and management (34,35). Rather than relying solely on the diagnosis of overt hyperglycemia, contemporary strategies emphasize the identification of metabolic dysfunction during its subclinical stages, when pathological changes remain potentially reversible (33-36). Early risk stratification and prescreening have therefore become essential components of diabetes prevention, particularly among individuals with obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), hypertension, dyslipidemia, polycystic ovary syndrome, or a family history of diabetes (36,37). Current screening approaches integrate conventional glycemic markers, including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and the oral glucose tolerance test (OGTT), with comprehensive assessment of cardiometabolic risk factors to facilitate earlier diagnosis and timely intervention (35,38,39). This proactive strategy shifts the clinical focus from detecting established diabetes to identifying metabolic dysfunction before irreversible pancreatic β-cell damage and vascular complications occur.

The evolving understanding of T2DM pathogenesis has also influenced diagnostic criteria and therapeutic decision-making. Although hyperglycemia remains the cornerstone of diagnosis, increasing evidence suggests that glycemic indices alone do not adequately reflect the complexity or heterogeneity of metabolic dysfunction (40,41). Consequently, a more comprehensive evaluation incorporating obesity phenotype, insulin resistance, lipid metabolism, inflammatory status, hepatic and renal function, and cardiovascular risk is increasingly advocated to guide individualized treatment (26,37,42). Preventing disease progression now extends beyond achieving glycemic targets and instead prioritizes preserving β-cell function, reducing chronic inflammation, improving insulin sensitivity, and minimizing long-term cardiovascular and renal complications (38,43). These objectives have been facilitated by the availability of novel pharmacological agents, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as Tirzepatid and Retatrutide, whose therapeutic benefits extend beyond glucose lowering to include weight reduction and cardiorenal protection (37,44). Consequently, current treatment algorithms increasingly adopt a personalized

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medicine approach that considers patient-specific metabolic characteristics, comorbidities, and organ involvement rather than relying on a uniform glucose-centered strategy (35,44).

Ultimately, the MDS framework supports a holistic model of diabetes care, integrating lifestyle modification, early metabolic risk assessment, individualized pharmacotherapy, and continuous monitoring of disease progression. This multidimensional approach recognizes that effective T2DM management requires coordinated interventions targeting multiple pathogenic pathways rather than isolated correction of hyperglycemia. By combining early diagnosis, prevention of metabolic deterioration, and personalized therapeutic strategies, the MDS paradigm provides a foundation for disease-modifying interventions aimed at delaying progression, reducing complications, and improving long-term clinical outcomes.

3 Conclusion

Type 2 diabetes mellitus (T2DM) is increasingly recognized as a manifestation of MDS, reflecting a complex interplay of insulin resistance, β-cell dysfunction, chronic inflammation, metabolic stress, and inter-organ dysregulation rather than hyperglycemia alone. This paradigm shift supports a more comprehensive approach to diabetes management, emphasizing early risk identification, timely diagnosis, prevention of disease progression, and personalized therapeutic strategies that address the underlying metabolic abnormalities. Ultimately, integrating the MDS framework into clinical practice may facilitate more effective disease-modifying interventions, improve long-term cardiometabolic outcomes, and reduce the global burden of T2DM.

4 Declarations

4.1 Acknowledgement

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4.2 Author Contribution

DC conducted the experiments, performed cell culture, and prepared the manuscript. DRA, HH analysed the data and contributed to manuscript preparation. NH supervised the study and provided scientific guidance. YA collected patient samples and assisted with the ethical approval process.

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