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Review

Metabolic Syndrome in 2025: Pathophysiology, Multi-Organ Crosstalk, and Emerging Therapeutic Strategies

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Abstract

The global burden of metabolic diseases has increased substantially, positioning metabolic syndrome as a major public health concern. It comprises a cluster of interrelated conditions, including type 2 diabetes mellitus, obesity, dyslipidemia, hypertension, and metabolic dysfunction-associated steatotic liver disease, driven by genetic, environmental, and lifestyle factors. This review provides an updated synthesis (2025) of the pathophysiological mechanisms underlying metabolic syndrome, with emphasis on insulin resistance as a central contributor to metabolic dysfunction. Key processes including beta-cell dysfunction, adipose tissue inflammation, and multi-organ crosstalk are discussed to illustrate the systems-level nature of the disease. Therapeutic strategies are examined, highlighting advances in incretin-based therapies and SGLT2 inhibitors, which have demonstrated significant benefits in glycemic control, weight reduction, and cardiovascular and renal outcomes. Emerging areas, including immunometabolism, gut microbiome interactions, and the integration of artificial intelligence with multi-omics technologies, are also considered, with attention to their current limitations and translational status. Overall, this review integrates mechanistic insights with clinical advances to provide a comprehensive perspective on metabolic syndrome and its evolving management in the era of precision medicine.

Keywords

Metabolic syndrome, Type 2 diabetes mellitus, Obesity, Dyslipidemia, Metabolic dysfunction-associated steatotic liver disease, Immunometabolism, Gut microbiome, Artificial intelligence, Multi-omics

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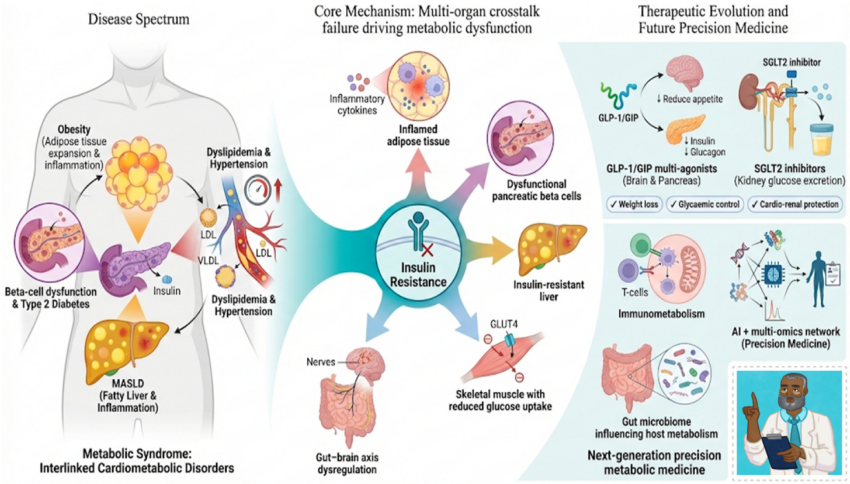
Graphical Abstract



1. Introduction

1.1 Defining a Modern Pandemic

Metabolic syndrome (MetS) is essentially not one solitary disease. It is a cluster of cardiometabolic risk factors that considerably elevate an individual's probability of atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes mellitus (T2DM), and mortality from any cause [1,2]. While various health organizations present different diagnostic criteria for metabolic syndrome, the primary aspects are essentially the same: excessive fat around the waist (based on the waist circumference), high blood sugar (elevated fasting glucose), abnormal blood lipids (mainly high triglycerides and low high-density lipoprotein cholesterol [HDL-C]) and elevated blood pressure. Usually, the presence of any three out of these five components is sufficient to diagnose a person with MetS. The medical importance of such a combination is quite substantial [3,4]. The risk that MetS brings is higher than the sum of the individual components. This indicates a shared pathophysiology. A person with MetS has 5 times higher chances of T2DM and 2 times higher chances of cardiovascular disease within the next 5-10 years. The worldwide prevalence of MetS is very much unquiet, and it affects about 25-35% of the adult population in developed countries. Developing countries, however, are witnessing disturbing increases as they get adapted to the Western lifestyles. Hence, MetS becomes a leading source of global health problems, deaths, and the rising costs of healthcare. It puts an enormous and, thus, unsustainable burden on both individuals and societies. The origins of this pandemic are very much linked to the contemporary environment. It is a consequence of a combination of sedentary lifestyles, overconsumption of energy-dense, heavily processed foods, and a complex set of social and economic factors [5].

1.2 Insulin Resistance: The Central Hub of Metabolic Dysfunction

While MetS is a multifaceted condition, Stages of research have shown that insulin resistance is the main problem from which most other issues arise [6,7]. Insulin resistance is widely recognized as a central contributor to metabolic dysfunction, although its relative importance varies across individuals and disease phenotypes. Insulin is the most important hormone out of the pancreatic beta cells. While the role of insulin resistance is well-established, much of the mechanistic evidence derives from experimental and animal models, and its precise contribution relative to other drivers of metabolic syndrome in humans remains context dependent. It is essential in regulating glucose levels in the body. For instance, it allows glucose to enter the cells and then keeps it in the form of glycogen in the muscle and fat tissues. Moreover, it reduces the glucose that the liver makes and oversees fat metabolism. When the target tissues involved in the glucose metabolism do not react normally to insulin in the blood, the patient is said to have insulin resistance. The genesis of insulin resistance is not straight forward; however, it is tightly coupled with body fat, particularly with the deposit of visceral adipose tissue. Visceral fat, in contrast to subcutaneous fat, is not a passive receptor but an endocrine organ that can eventually become dysfunctional if over-nutrition continues. This fat is changed in many ways; for example, the size of the fat cells is increased, there is a shortage of oxygen, and the immune cells infiltrate it, which causes it to become inflamed. Consequently, chronic low-grade inflammation or "metaflammation" is the result of this process. The inflamed adipocytes secrete different pro-inflammatory cytokines, for instance, TNF-α and IL-6, and, in addition, they discharge more free fatty acids (FFAs) into the blood circulation than normal [8,9]. Such substances meddle with insulin signaling in peripheral tissues such as the liver and skeletal muscle by blocking the insulin receptor substrate (IRS)-PI3K-Akt signaling pathway. The interruption of this pathway is the primary cause of insulin resistance. As resistance is going to be developed, the pancreas will make a compensation by increasing insulin secretion to keep blood sugar levels normal. This fragile balance can still be maintained for a while. Although, this elevated insulin condition may be the cause of additional problems related to MetS. It facilitates sodium retention in the kidneys leading to hypertension and it also encourages liver fat production, thereby, making the levels of fat in the blood worse. At some point, the overwhelming and continuous demand for beta cells will result in their decline and death. Therefore, this is the point when a person moves from compensated insulin resistance to type 2 diabetes [10,11]. Although chronic low-grade inflammation is consistently associated with metabolic dysfunction, causal relationships remain difficult to establish due to overlapping metabolic and immune pathways.

Although metabolic syndrome, insulin resistance, and MASLD are closely interrelated, they represent distinct conceptual entities. Metabolic syndrome is a clinical construct defined by the co-occurrence of cardiometabolic risk factors, including central obesity, hyperglycemia, dyslipidemia, and hypertension. In contrast, insulin resistance is a core pathophysiological mechanism that contributes to the development of these abnormalities but is not itself a clinical diagnosis. MASLD represents an organ-specific manifestation of metabolic dysfunction, characterized by ectopic lipid accumulation in the liver and driven in part by insulin resistance and systemic metabolic imbalance. Distinguishing these concepts is essential for understanding the heterogeneity of metabolic disease and for developing targeted therapeutic strategies.

1.3 A Paradigm of Multi-Organ Crosstalk Failure

Since 2025, the concept of MetS has changed significantly. Initially, the main focus was only on insulin resistance but now it is considered a disease in which crosstalk between organs is impaired [12,13]. The body usually keeps its balance through a delicately coordinated signaling network that involves the pancreas, liver, fat tissue, skeletal muscle,

gut, and brain. In the case of MetS, this interaction stoppage is one of the factors. Fat tissue that does not function properly releases an excessive amount of FFAs to the liver. As a result, liver fat accumulation, a greater production of very low-density lipoproteins (VLDL), and the beginning of liver insulin resistance occur [14,15]. Meanwhile, disruptions in the gut-brain axis that are caused by a decreased incretin signaling (e.g. GLP-1) and changes in signals from gut microbiota, result in bad signals of satiety and reduced insulin secretion. Pro-inflammatory adipokines released from the fat tissue interfere with insulin-stimulated glucose uptake in skeletal muscle, which is the primary organ for postprandial glucose management [16,17]. Moreover, the diminution in signaling from the central nervous system to adipose tissue that is in part a consequence of leptin resistance in the hypothalamus, changes the mechanisms of energy expenditure and fat accumulation. This condition, therefore, favors the uninterrupted positive energy balance. Such complex entanglements emphasize the necessity of a bolder approach to grasp the concept of MetS. The interconnected pathophysiological network underlying metabolic syndrome, linking visceral adiposity, insulin resistance, dyslipidaemia, chronic inflammation, and downstream cardiometabolic complications, is schematically illustrated in Figure 1. These interconnected signaling disruptions ultimately manifest as distinct but overlapping clinical conditions, which together define the spectrum of metabolic syndrome. The side effects of this conglomerate of metabolic risk factors stem from a general malfunction of the body, thus the therapeutic methods that target only one pathway seldom bring the restoration of the clinical condition for a prolonged period [18,19]. The principal axes of inter-organ crosstalk disruption and their molecular mediators contributing to insulin resistance, dyslipidemia, and ectopic lipid accumulation are summarized in Table 1. To understand the clinical manifestations of metabolic syndrome, it is essential to first examine the underlying molecular and cellular mechanisms that drive insulin resistance and systemic metabolic dysfunction.

Table 1. Key organ-organ crosstalk pathways and molecular mediators driving metabolic syndrome.

Organ Axis	Primary Mediators	Pathophysiological Consequence	Clinical Manifestation
Adipose → Liver	FFAs, TNF-α, IL-6	Hepatic insulin resistance, increased VLDL secretion	Dyslipidemia, MASLD
Adipose → Skeletal Muscle	Pro-inflammatory adipokines	Impaired insulin-stimulated glucose uptake	Postprandial hyperglycemia
Gut → Brain	Reduced GLP-1, altered short-chain fatty acids (SCFAs)	Impaired satiety signaling, appetite dysregulation	Obesity
Gut → Systemic Circulation	LPS (endotoxemia), reduced barrier integrity	Low-grade systemic inflammation	Insulin resistance
Brain → Adipose	Leptin resistance	Reduced energy expenditure, increased fat storage	Positive energy balance
Liver → Systemic	Excess VLDL, glucose overproduction	Atherogenic dyslipidemia, hyperglycemia	ASCVD risk

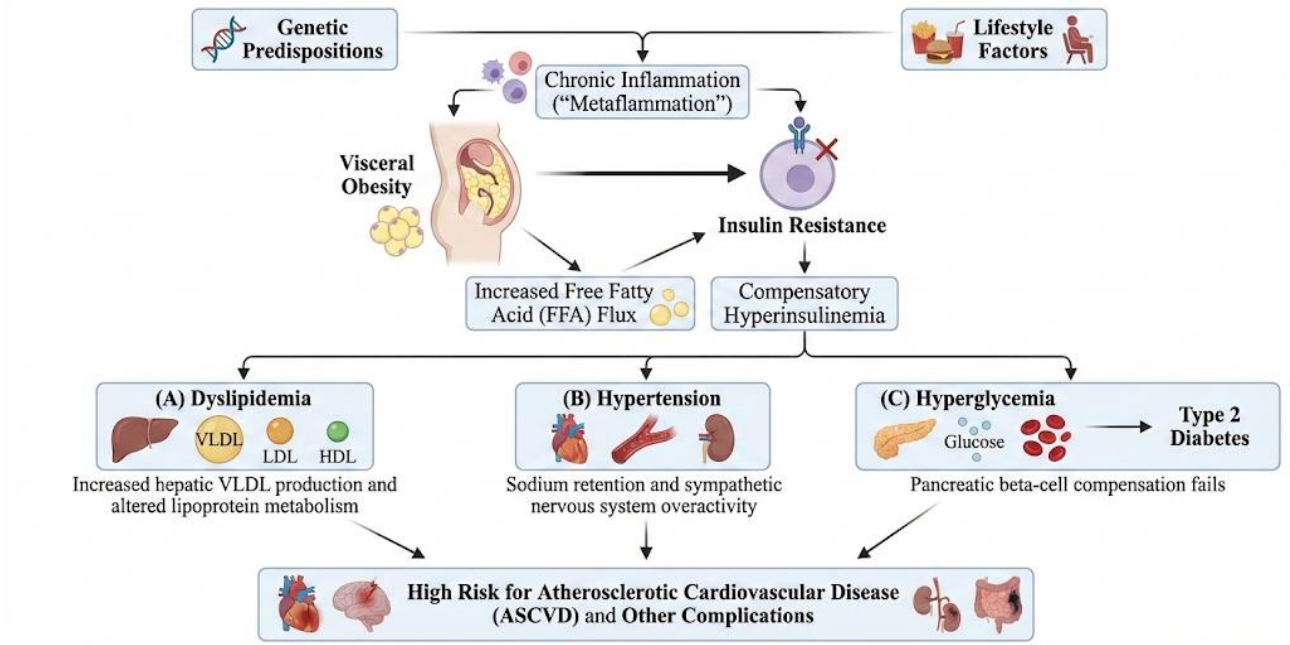


Figure 1. The interconnected pathophysiology of metabolic syndrome.

1.4 Objectives of the Review

This review aims to provide a comprehensive and integrative synthesis of metabolic syndrome as a systems-level disorder. Specifically, it seeks to: (i) elucidate the central role of insulin resistance and its molecular underpinnings, (ii) characterize multi-organ crosstalk and the signaling networks linking metabolic tissues, (iii) examine the progression of key disease domains including T2MD, dyslipidemia, hypertension, and MASLD, and (iv) critically evaluate current and emerging therapeutic strategies, including incretin-based therapies, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and precision medicine approaches driven by artificial intelligence (AI) and multi-omics integration.

2. Literature Search and Selection Strategy

This narrative review was conducted using a structured literature search to ensure comprehensive coverage of current evidence related to metabolic syndrome and its multi-organ pathophysiology. Electronic databases including PubMed, Scopus, and Web of Science were systematically searched for relevant articles published between 2015 and 2025, with priority given to studies published in the last five years.

The search strategy incorporated combinations of keywords and Medical Subject Headings terms such as: “metabolic syndrome”, “insulin resistance”, “organ crosstalk”, “immunometabolism”, “gut microbiome”, “MASLD”, “GLP-1 receptor (GLP-1R) agonists”, “SGLT2 inhibitors”, “multi-omics”, and “artificial intelligence in metabolic disease”.

Studies were selected based on relevance to the mechanistic understanding and clinical management of metabolic syndrome. Inclusion criteria comprised original research articles, clinical trials, systematic reviews, and high-impact narrative reviews published in peer-reviewed journals. Exclusion criteria included non-English publications, case reports, conference abstracts without full data, and studies lacking clear methodological rigor.

Emphasis was placed on integrating high-quality primary studies, landmark clinical trials, and recent advances to ensure both depth and contemporary relevance. Reference lists of selected articles were also screened to identify additional pertinent studies.

2.1 The Pathophysiology of Beta-Cell Dysfunction

The transition from compensated insulin resistance to T2DM is when pancreatic beta cells can no longer maintain their high secretion levels. The switch is not abrupt but gradual and is determined by multiple stressors. The term for this is glucolipotoxicity [20,21]. Eventually, exposure to high glucose levels (glucotoxicity) combined with elevated FFAs (lipotoxicity) has a direct damaging effect on beta cells. A rise in glucose concentration stimulates the metabolic flux through the beta cell. As a result, the excessive production of reactive oxygen species (ROS) occurs, and the cell experiences stress in the endoplasmic reticulum due to the increased demand of insulin production and folding [22,23]. Saturated FFAs may transform into perilous lipid species such as ceramides that lead to programmed cell death (apoptosis). On top of that, the deposition of islet amyloid polypeptide also takes place. This peptide is co-released with insulin and thus generates toxic oligomers and amyloid plaques around the beta cells, which damages them even more. The continuous assault of this kind on cells causes the gradual decrease of both beta-cell function, which comprises defective glucose sensing and insulin secretion, as well as beta-cell mass. The reduction hereof finally brings about the relative insulin deficiency that characterizes T2DM [24]. An improved understanding of these disease processes has directly informed the development of targeted therapeutic strategies aimed at modifying both metabolic pathways and organ-level dysfunction.

2.2 A Historical Perspective on Therapeutics

Over the years, our understanding of T2DM and its treatments has changed as evidenced by when the first pharmacotherapy (oral medication) for T2DM was developed - producing ways to influence the function of a declining pancreas (increased secretion) or by providing the body with "added" or "external" insulin [25,26]. Sulfonylureas such as glipizide and meglitinides act in a similar manner by shutting down the ATP-sensitive potassium (K-ATP) channel located on the beta cell. The result is depolarization and insulin release. Still, they carry a significant risk of hypoglycaemia and may cause beta-cell exhaustion. The traditional first-line drug, metformin, mainly works by lowering glucose production in the liver and has a small insulin-sensitizing effect in the peripheral tissues. The detailed molecular mechanisms, such as its effect on mitochondrial complex I and AMPK activation, are still being resolved [27,28]. The next wave of drugs also aimed to tackle insulin resistance in a more direct manner. One of the main insulin-sensitizing agents is a group of medications called thiazolidinediones (TZDs) with pioglitazone being one of them. They bind with and activate the PPARγ nuclear receptor, which is a protein highly abundant in m-Fat cells. TZDs promote the generation of smaller, more insulin-sensitive fat cells. Besides, they make fat storage change from the belly area to under the skin. This process, in fact, helps with reducing lipotoxicity. Nevertheless, the employment of TZDs has been curtailed owing to side effects such as weight gain, edema, and bone fractures [29,30]. Despite these advances, current therapies do not fully address the complexity and heterogeneity of metabolic disease, prompting exploration of emerging concepts that extend beyond traditional pharmacology.

2.3 Progression from Insulin Resistance to Clinical Disease

Building on the molecular mechanisms of insulin resistance, the progression toward overt metabolic disease involves a continuum of compensatory and maladaptive responses. Early hyperinsulinemia maintains glucose homeostasis; however, persistent metabolic stress leads to beta-cell dysfunction, glucolipotoxicity, and systemic metabolic imbalance. This transition marks the shift from subclinical metabolic dysregulation to clinically manifest conditions such as T2MD and associated cardiometabolic complications.

2.4 The Incretin Revolution: GLP-1R Agonists and DPP-4 Inhibitors

Despite robust clinical trial outcomes, long-term safety, durability of weight loss, and real-world adherence remain areas requiring further investigation. The rant about the poor incretin system has finally been resolved with the treatment. Dipeptidyl peptidase-4 (DPP-4) inhibitors, for instance, sitagliptin, block the degradation of endogenous GLP-1 and GIP. As a result, the body's natural incretin response is improved [31,32]. Such medications can be taken by mouth and do not cause weight gain, with the risk of hypoglycemia being very low. Nevertheless, their glucose-lowering effect is only slight. It wasn't until the development of injectable GLP-1R agonists, like liraglutide and semaglutide, that the real breakthrough occurred. These drugs behave like natural GLP-1, thus they provide insulin release and glucagon suppression that are both strong and dependent on glucose. Moreover, their potent effects on the brain help decrease appetite and raise satiety, thereby resulting in a noteworthy and, most importantly, a weight loss that is maintained for a long time. Thus, this is a direct approach to the problem of obesity. The latest generation of these pharmaceuticals comprises multi-agonists [33-35]. The medication that was given the green light in 2022, Tirzepatide, is a dual agonist for both the GLP-1R and GIP receptor. It can achieve astounding levels of glycemic control and weight reduction practically to the level of bariatric surgery have been shown in the landmark trials including SURPASS as well as SURMOUNT. Late-stage clinical trials of even more complicated tri-agonists targeting GLP-1, GIP, and glucagon receptors, such as retatrutide, were reported as of early 2025. They have indicated more than 24% average weight loss and are very promising for the treatment of obesity, diabetes, and the related disorders such as MASLD [36]. The mechanistic targets, principal organ sites of action, and dominant clinical benefits of established and emerging pharmacological classes used in metabolic disease management are summarized in Table 2. The clinical efficacy of dual incretin agonism has been robustly demonstrated in the SURPASS clinical trial program, where tirzepatide achieved superior glycemic control and weight reduction compared to insulin and GLP-1R agonists. In parallel, the SURMOUNT trials reported substantial weight loss exceeding 20% in patients with obesity, highlighting its potential to modify disease trajectory beyond glycemic control.

Table 2. Major therapeutic classes in metabolic disease and their primary mechanistic targets and organ-level benefits.

Drug Class	Representative Agents	Primary Mechanism	Dominant Organ Target	Key Clinical Benefit
Biguanides	Metformin	Inhibits hepatic gluconeogenesis; AMPK activation	Liver	Improves insulin sensitivity
GLP-1R Agonists	Semaglutide, Liraglutide	Enhances insulin secretion; suppresses appetite	Brain, Pancreas, Gut	Weight loss, glycemic control
Dual GLP-1/GIP Agonists	Tirzepatide	Synergistic incretin signaling	Brain, Pancreas	Profound weight loss, T2DM remission
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	Renal glucose excretion	Kidney, Heart	Cardio-renal protection
PPARγ Agonists (TZDs)	Pioglitazone	Adipocyte insulin sensitization	Adipose tissue	Improved insulin sensitivity
Thyroid Hormone Receptor-β Agonists	Resmetirom	Enhances hepatic lipid oxidation	Liver	MASLD/MASH improvement

2.5 The Rise of the SGLT2 Inhibitors: A New Cardio-Renal Paradigm

While the incretin revolution was going on, a new class of drugs appeared that work differently. SGLT2 inhibitors, such as empagliflozin and dapagliflozin, are agents that act in the proximal tubule of the kidney [37,38]. Although cardiovascular and renal benefits are well supported by large, randomized trials, the exact mechanisms underlying these effects remain incompletely understood. They prevent glucose from being absorbed again, so glucose in excess is excreted with urine, which is called glycosuria. This is an insulin-independent mechanism that helps to normalize blood glucose levels efficiently and with a very low risk of hypoglycaemia. At the same time, it causes a slight decrease in body weight and a reduction in blood pressure due to the osmotic diuretic effect. It was amazing that essential and largely unexpected beneficial effects of such drugs on the heart and kidneys [39,40]. Large-scale cardiovascular outcome trials such as EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF have unequivocally demonstrated that SGLT2 inhibitors are very effective in reducing the risk of major adverse cardiovascular events, hospitalizations for heart failure, and the progression of chronic kidney disease in both diabetic and non-diabetic individuals. These improvements are far from what could be accounted for by glycemic control alone. They are most likely the result of a complicated interplay of different factors including hemodynamic changes (less preload and

afterload), metabolic changes (inducing a mild state of ketosis which is a better source of energy for the heart), and direct effects on inflammation and fibrosis of the heart and kidneys. [41,42]. It has altered the way we comprehend T2DM to be a condition that mainly causes damage to the heart, kidneys, and metabolism. The complementary mechanisms of incretin-based multi-agonists and SGLT2 inhibitors, acting through central appetite regulation, pancreatic hormone modulation, gastrointestinal motility, and renal glucose excretion, are illustrated in Figure 2. Consequently, the standards of care put more emphasis on employing medications such as SGLT2 inhibitors and GLP-1R agonists which have been shown to have organ-protective effects, thus their use is not limited to patients with certain HbA1c levels only [43]. While these mechanisms provide a molecular foundation, metabolic syndrome cannot be fully explained by isolated pathways, as it arises from dynamic interactions between multiple organs. Large-scale randomized controlled trials have firmly established the cardio-renal benefits of SGLT2 inhibitors. The EMPA-REG OUTCOME trial demonstrated a significant reduction in cardiovascular mortality with empagliflozin, while the DECLARE-TIMI 58 and DAPA-HF trials confirmed reductions in heart failure hospitalization and progression of chronic kidney disease, including in non-diabetic populations.

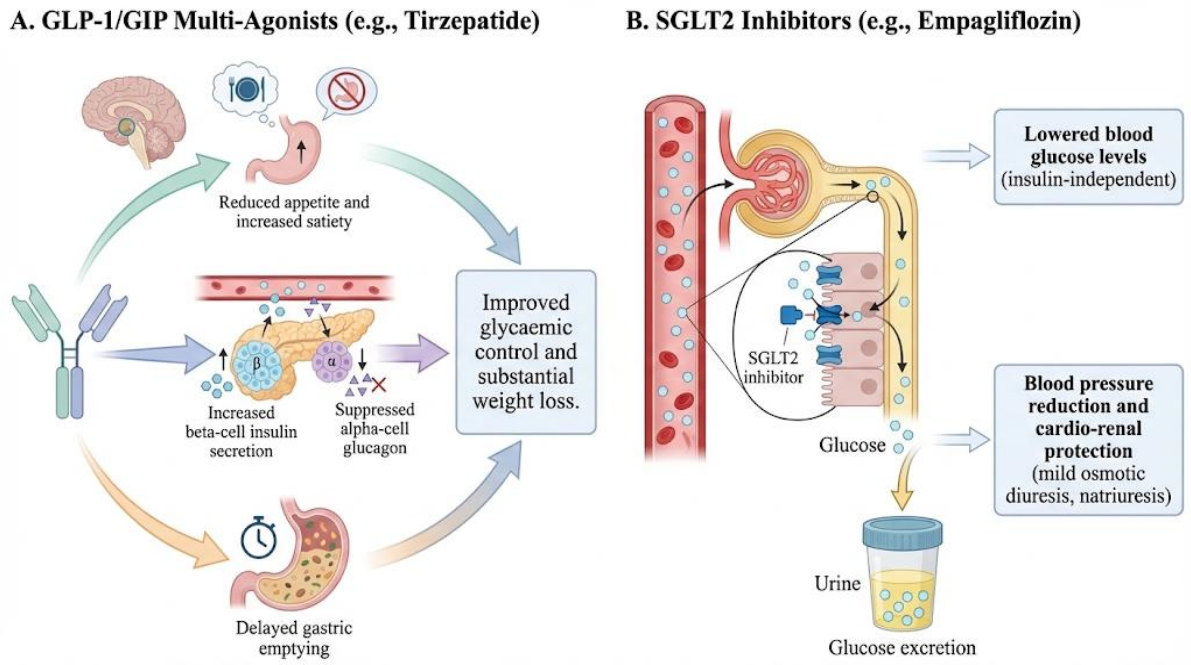


Figure 2. Mechanisms of action of revolutionary anti-diabetic drug classes. (A) GLP-1/GIP multi-agonists (e.g., Tirzepatide). (B) SGLT2 inhibitors (e.g., Empagliflozin).

3. Multi-Organ Crosstalk: Dyslipidemia and Hypertension

3.1 Atherogenic Dyslipidemia: More than just High Cholesterol

The dyslipidemia of MetS and T2DM that is different from familial hypercholesterolemia has been frequently referred to as atherogenic dyslipidemia. The scenario is not that of a very high concentration of low-density lipoprotein cholesterol (LDL-C) which in fact can be in the normal range or only slightly increased [44-46]. Rather, it is characterized by a specific set of parameters such as elevated triglycerides, decreased levels of HDL-C, and a change in LDL composition towards small, dense particles. These small, dense LDL particles are more susceptible to oxidative changes and can more easily infiltrate the arterial wall. Consequently, atherosclerosis risk is higher, even if LDL-C levels are within the normal range. This detrimental lipid profile is essentially a consequence of insulin resistance in the liver. When the body is insulin resistant, insulin does not inhibit fat breakdown in fat tissue. As a result, there is a continuous supply of FFAs to the liver. Moreover, elevated insulin levels signal the liver to produce more fat via a process called lipogenesis [47-49]. This additional fat causes the liver to release an excessive amount of VLDL particles that are filled with triglycerides. Once in the blood, cholesteryl ester transfer protein mediates the exchange of some of the triglycerides in these VLDL particles with the cholesteryl esters that it finds in HDL and LDL particles. The exchange generates HDL particles that are rich in triglycerides and rapidly cleared from the circulation, thus reducing HDL-C. It also generates triglyceride-rich LDL particles that are converted by hepatic lipase into small, dense LDL particles. These small, dense LDL particles are very harmful, first of all, because they can easily penetrate the artery lining, secondly, they are more susceptible to oxidation, and thirdly, they have a lower affinity for the LDL receptor. Thus, they are retained for a longer time in the bloodstream [50,51].

Lifestyle changes are the primary treatment for atherogenic dyslipidemia. Statins are very powerful in decreasing LDL-C by inhibiting HMG-CoA reductase and thus are used if necessary. In the case of extreme hypertriglyceridemia, the physician may administer fibrates (PPARα agonists) or large amounts of omega-3 fatty acids. Additionally, novel drugs

that specifically target ANGPTL3 and apoC-III are also becoming less hesitant as potent triglyceride-lowering agents [52,53].

3.2 Hypertension in Metabolic Syndrome: A Multifactorial Challenge

The connection between insulin resistance and high blood pressure in MetS is a complicated one, and the causality can be traced in both directions. It is due to a combination of intertwined mechanisms that blood pressure is elevated [54,55]. Prolonged high insulin levels promote the retention of sodium and water in the kidneys through reabsorption, thus increasing blood volume. Besides that, insulin resistance and elevated leptin levels also stimulate the sympathetic nervous system. Consequently, the heart rate and cardiac output become higher, and the blood vessels constrict more, leading to an increase in blood pressure [56,57]. At the same time, malfunctioning fat tissue raises the activity of the renin-angiotensin-aldosterone system through increased production of angiotensinogen as well as by intensifying intrarenal and vascular renin-angiotensin-aldosterone system (RAAS) signaling. As a consequence, this brings about vasoconstriction and sodium retention even more. These effects on the circulation system become aggravated by endothelial dysfunction. Under such conditions elevated glucose and increased levels of FFAs lead to the generation of ROS and the development of an inflammatory process in the vascular endothelium [58-60]. This reduces the availability of nitric oxide and thus makes the vascular tone to be in a state of constant constriction. The treatment of hypertension in MetS is according to the usual standard guidelines. RAAS inhibitors, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are put first in the line of treatment because of their good metabolic and protective effects on the kidneys. Calcium channel blockers and thiazide diuretics are also frequently used. What is more, these new metabolic drugs also offer some benefits for blood pressure. GLP-1R agonists help to lower blood pressure via such mechanisms as natriuresis and slight weight reduction. SGLT2 inhibitors contribute to blood pressure lowering especially due to their osmotic diuretic action [61-63].

3.3 Obesity and MASLD: The Core and Consequence of Energy Overload

3.3.1 Adipose Tissue as a Dysfunctional Endocrine Organ

The modern perspective of obesity has altered. It is not simply considered one of being overweight anymore. Rather, it is recognized as a long-term, comeback disease that is associated with a dead organ: fat tissue [64-66]. Under healthy conditions, adipose tissue is the main organ that can store the excess energy in the form of triglycerides and release the most helpful type of substances called adipokines. To give an example, adiponectin is the one that has very strong anti-inflammatory and insulin-sensitizing effects. Obesity development is an adipocyte enlargement beyond their usual capacity, also called hypertrophy. The increase in the size of adipocytes causes mechanical stress, reduces blood flow, and finally, cell death occurs. The cell death causes the tissue infiltration of immune cells, especially macrophages, in very large numbers. These macrophages convert from anti-inflammatory "M2" to pro-inflammatory "M1" phenotype, hence the occurrence of metaflammation, an inflammatory state associated with metabolism [67-69]. This inflamed fat tissue becomes resistant to insulin and changes its secretion pattern. The production of the helpful hormone adiponectin is reduced dramatically, while the release of the harmful pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, as well as the production of the damaging adipokines such as leptin and resistin, increases greatly. One of the factors that cause the brain to keep a positive energy balance is its resistance to leptin, even though high levels of this hormone are found in the blood. There is no reduction in appetite and no increase in energy expenditure. Recent phase II and III clinical trials have further supported the therapeutic potential of metabolic-targeting agents in MASLD/MASH, with GLP-1R agonists demonstrating histological improvement in steatohepatitis and fibrosis resolution in a subset of patients. As outlined earlier, insulin resistance serves as a central mechanistic link connecting systemic metabolic dysfunction with hepatic lipid accumulation. This dysfunctional state is the one that drives the widespread insulin resistance and inflammation that are at the root of all other aspects of MetS [70,71].

3.3.2 From Non-Alcoholic Fatty Liver Disease (NAFLD) to MASLD: A Disease of Ectopic Fat

Once the storage capacity of subcutaneous fat tissue is surpassed; lipids are going to be spilled and accumulated in non-fat tissues. This phenomenon is known as ectopic fat deposition or lipotoxicity. The liver is the organ that is most affected by this process [72-74]. The accumulation of fat in the liver, in the absence of overconsumption of alcohol, was formerly referred to as NAFLD. In 2023, an international expert panel agreed to rename the condition to MASLD. This is a more accurate description of the condition as the liver's reaction to metabolic syndrome. MASLD can be seen as a spectrum. The very first stage is just the presence of fat in the liver, which is essentially a safe condition [75-77]. Nevertheless, this may develop in some individuals to metabolic dysfunction-associated steatohepatitis, abbreviated as MASH. MASH is a significant progression of the condition, characterised by the irritation and enlargement of liver cells. MASH causes worry as it can lead to liver fibrosis, i.e. scarring of the liver, due to inflammation and damage to cells that occur over a long period of time. Eventually, this fibrosis can turn into cirrhosis, liver failure at its final stage, and hepatocellular carcinoma, the major type of liver cancer, according to which liver transplantation due to MASH will be the leading cause worldwide by 2025 [78-80]. The evolution of MASH is generally illustrated by the "multiple hit" hypothesis. The "first hit" is the fat accumulation in the liver which is a result of insulin resistance and increased free fatty acid flow. The "second hits" are a variety of factors. They are oxidative stress due to mitochondrial dysfunction,

endoplasmic reticulum stress caused by fat toxicity, inflammatory signals induced by gut-derived endotoxins, and signaling from pro-inflammatory cytokines. Thus, these factors comprise the necroinflammatory process that causes fibrosis [81].

3.3.3 The Therapeutic Frontier for MASH

Although MASH was everywhere and had very serious impacts, there were no FDA-approved drugs that targeted it specifically until quite recently. In 2024, the FDA granted accelerated approval to resmetirom, a drug that binds to thyroid hormone receptor-beta and thereby increases liver fat metabolism [82-84]. This was a very important landmark. The pipeline for therapies is now very vibrant. The most promising agents are those that essentially focus on the main metabolic causes of the disease. One example is GLP-1R agonists like semaglutide and multi-agonists like tirzepatide that have demonstrated impressive effectiveness in MASH resolution and fibrosis improvement as they help with weight loss and reduce liver lipotoxicity. Besides these, there are also FXR agonists, such as obeticholic acid, that regulate bile acid production and lessen the inflammation. In addition, CCR2/5 inhibitors are there which stop inflammatory monocytes from migrating to the liver. The next generation of MASH therapy will probably be combination regimens that target metabolism, inflammation, and fibrosis simultaneously [85].

In addition to classical signaling pathways, circulating organokines-including adipokines, myokines, and cardiokines-serve as key mediators of inter-organ metabolic communication. Adipokines such as adiponectin exert insulin-sensitizing and anti-inflammatory effects, whereas others, including fatty acid-binding protein 4 (FABP4), are associated with insulin resistance and atherogenic processes. Similarly, myokines such as irisin link skeletal muscle activity to systemic energy homeostasis, while cardiokines like follistatin-like 1 (FSTL1) contribute to cardiovascular and metabolic regulation.

Recent clinical evidence highlights the diagnostic and integrative value of these molecules. For instance, combined profiling of adiponectin, irisin, and FSTL1 has demonstrated high diagnostic performance in identifying metabolic syndrome, reflecting the coordinated dysfunction of multiple organs. Furthermore, emerging studies utilizing machine learning approaches suggest that organokine networks can be modeled to predict disease risk and inter-organ signaling patterns. These findings reinforce the concept that metabolic syndrome is not only a disorder of individual tissues but also a disruption of a dynamic, circulating signaling network.

4. Emerging Directions

The field of metabolic disease is rapidly changing due to technological advances and new ideas. Research today focuses on the complex systems that control homeostasis, moving past single organs and pathways.

4.1 Immunometabolism: The Immune System as a Metabolic Rheostat

A major emerging paradigm is the emergence of immunometabolism, which studies the communication between the immune and metabolic systems. The immune system is no longer considered to be a mere responder to metabolic stress as it is shown that it is an active regulator of metabolic homeostasis [86,87]. Immune cells are equipped with a range of receptors that can not only identify metabolic substances such as glucose, fatty acids, and amino acids but also recognize metabolic hormones like insulin and leptin. With this capability, immune cells are able to modify their operation according to the metabolic state of the organism. Thus, effector T cells in a nutrient-rich milieu escalate glycolysis to energize their fast proliferation and pro-inflammatory activities. On the other hand, regulatory T cells in nutrient-deficient milieus rely on fatty acid oxidation to retain their immunosuppressive functions. Such a link implies that the continuous nutrient overabundance of MetS alters the immune system in a way that it becomes pro-inflammatory [88,89]. The local inflammatory response of macrophages in adipose tissue is only part of the story. A systemic pro-inflammatory shift is a major contributor to endothelial dysfunction in blood vessels, beta-cell damage in the pancreas, and inflammatory injury in the liver and kidneys. This concept broadens the horizon of treatment options tremendously. The next-generation drugs might no longer be limited to the metabolic pathways but rather they could work to "reprogram" the immune system to a metabolically healthy, anti-inflammatory state again. An example of such an approach would be the targeting of certain metabolic checkpoints in immune cells [90].

4.2 The Gut Microbiome: A Neglected Endocrine Organ

The trillions of microorganisms that inhabit the human intestines, called the gut microbiome, have recently been identified as major environmental contributors to the onset of metabolic disease [91]. Current evidence linking gut microbiota to metabolic disease is largely associative, and variability between individuals limits the translation of these findings into standardized therapeutic interventions. The microbiome functions similarly to an endocrine organ in the sense that it produces a very diverse set of bioactive substances while digesting dietary components, notably fiber. These substances travel through the blood to various organs, thus sending them messages. The most researched are the SCFAs i.e. butyrate, propionate, and acetate [92]. Colonic cells use SCFAs as an energy source, enhance the intestinal wall's integrity, and signal through the activation of G protein-coupled receptors such as GPR41 and GPR43 across multiple cell kinds, including enteroendocrine L-cells [93]. These cells are the ones where the release of GLP-1 is

triggered. A properly functioning and varied microbiome that is effective in the production of SCFAs is associated with good metabolic health. In contrast, the gut microbiome of obese individuals with T2MD is characterized by reduced diversity (dysbiosis), and a shift towards bacteria that are more efficient in energy extraction and inflammation-inducing, according to several studies. In such an instance, a "leaky" gut barrier may allow bacterial constituents, for example, lipopolysaccharide (LPS), to reach the blood. Thereby, a low-grade systemic inflammatory response termed "metabolic endotoxemia" occurs, which is one of the factors causing insulin resistance [94,95]. These cells are the ones where the release of GLP-1 is triggered. The contrasting metabolic consequences of a eubiotic versus dysbiotic gut microbiome, including short-chain fatty acid production, incretin signalling, intestinal barrier integrity, and systemic inflammatory tone, are schematically depicted in Figure 3. In parallel with biological insights, technological advancements particularly in AI and multi-omics are reshaping how metabolic disease is characterized and managed.

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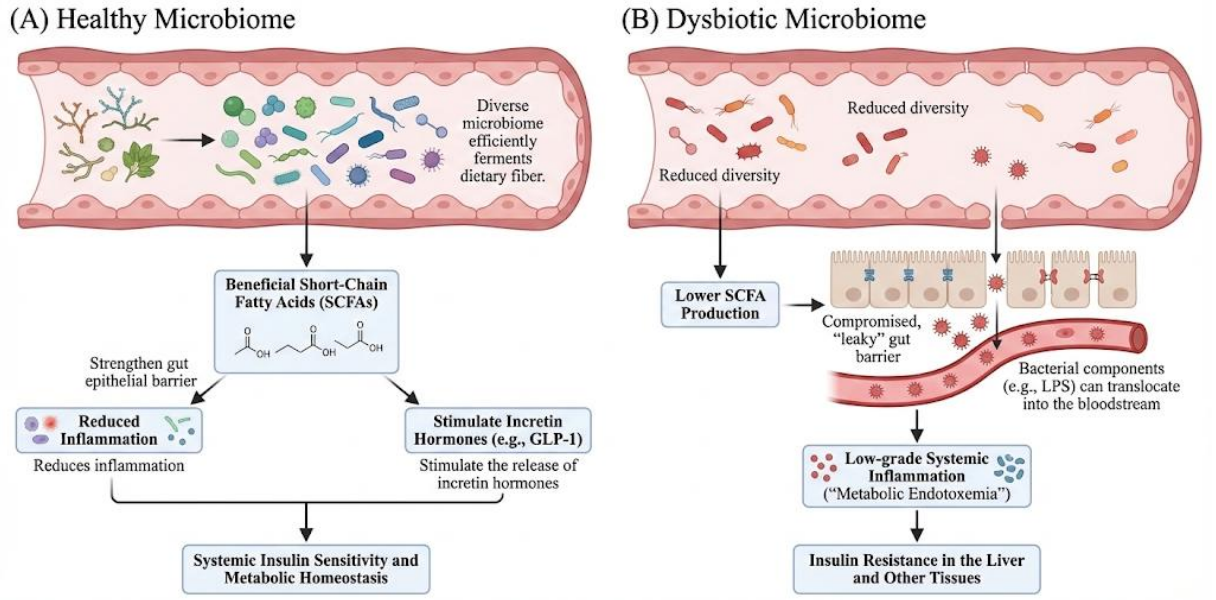

Figure 3. The role of the gut microbiome in metabolic health and disease. (A) Healthy microbiome. (B) Dysbiotic microbiome.

4.3 Personalized Medicine: The AI and Multi-Omics Revolution

Perhaps the most important trend shaping the future of metabolic medicine in 2025 is the integration of AI and multi-omics technologies to start a new era of true precision medicine [97]. Two individuals with T2DM may have received the diagnosis through very different biological processes; one may have primarily hepatic insulin resistance, while the other may have primary beta-cell failure. Yet, historically, they have been treated with the same protocols. Emerging studies integrating multi-omics datasets with machine learning models have demonstrated the ability to stratify patients into biologically distinct subtypes, improving prediction of disease progression and therapeutic response, although most applications remain at the translational or early clinical stage. After gathering huge datasets related to genomics, transcriptomics, proteomics, and metabolomics, scientists are gradually able to dissect MetS into separate molecular subtypes or "endotypes". To identify these complicated patterns in high-dimensional data, machine learning and deep learning algorithms play a vital role. The clinical implications of such sub-typing are quite profound [98].

AI is also transforming the pharmaceutical industry in a way that drugs are discovered. To illustrate our point, we mentioned GEN-101, and how generative AI platforms are able to come up with an entirely new drug candidate in a matter of seconds with a very specific set of properties, that are even pre-defined by the user. Innovation is thus accelerated to a very significant extent. Moreover, digital health platforms, wearable sensors, and continuous glucose monitors are becoming the sources of a large volume of real-world patient data. AI algorithms can shift through this data to provide very personalized lifestyle recommendations, predict hypoglycemic episodes, and create "digital twins" of patients to see how they will respond to different treatments, before patients actually receiving these treatments. [99,100]. Despite substantial advances, metabolic syndrome remains a heterogeneous condition, and variability in pathophysiology and treatment response underscores the need for individualized and evidence-calibrated approaches [101]. The clinical efficacy and evidence hierarchy of major therapeutic strategies in metabolic syndrome are summarized in Table 3, highlighting the strong support from large randomized controlled trials for incretin-based

therapies and SGLT2 inhibitors, alongside emerging evidence for microbiome- and AI-driven approaches. The application of AI in metabolic medicine spans a spectrum from clinically implemented tools to emerging investigational frameworks.

Table 3. Landmark clinical evidence supporting major therapeutic strategies in metabolic syndrome.

Therapeutic Class	Representative Agent	Key Trial	Study Type	Major Outcomes	Level of Evidence	Ref.
GLP-1R Agonists	Semaglutide	SUSTAIN/STEP	RCT	Significant HbA1c reduction, weight loss	High	[102]
Dual Incretin Agonist	Tirzepatide	SURPASS/SURMOUNT	RCT	Superior glycemic control, >20% weight loss	High	[103]
SGLT2 Inhibitors	Empagliflozin	EMPA-REG OUTCOME	RCT	↓ CV mortality, ↓ HF hospitalization	High	[104]
SGLT2 Inhibitors	Dapagliflozin	DAPA-HF	RCT	↓ heart failure progression (incl. non-diabetics)	High	[105]
MASLD Therapy	Resmetirom	Phase III trials	RCT	Improved liver histology, reduced steatosis	Moderate-High	[106]
Microbiome-based	Various	Meta-analyses	Mixed	Variable metabolic improvement	Emerging	[107]
AI/Multi-omics	-	Translational studies	Observational	Patient stratification, predictive modeling	Emerging	[108]

4.3.1 Current Clinical Applications

AI and multi-omics approaches are increasingly being integrated into clinical and translational workflows. Current applications include risk prediction models for T2MD and cardiovascular disease, analysis of continuous glucose monitoring data for personalized glycemic control, and patient stratification using multi-omics datasets [109]. Digital health platforms and wearable devices further enable real-time monitoring and data-driven clinical decision support. While these tools are not yet universally implemented, they are actively being incorporated into specialized clinical settings and research-driven healthcare systems [110].

4.3.2 Emerging and Investigational Directions

Beyond current applications, AI and multi-omics technologies hold significant potential to transform metabolic medicine. Emerging approaches aim to define molecular endotypes of metabolic syndrome, enabling highly individualized therapeutic strategies. Machine learning models are being developed to integrate genomics, proteomics, and metabolomics data for improved prediction of disease progression and treatment response. In addition, concepts such as digital twins and AI-driven drug discovery remain largely investigational, with most applications currently confined to early-stage or translational research. Despite their promise, challenges related to data standardization, interpretability, and clinical validation continue to limit widespread adoption.

5. Conclusion

The field of metabolic disease research and treatment has changed dramatically over the past decade and is at an exciting turning point in 2025. We have shifted from focusing solely on blood sugar levels in diabetes to a broader view that considers multiple organs involved in metabolic syndrome. We have advanced from treatments that only manage high blood sugar to innovative agents that cause significant weight loss, reverse liver fat accumulation, and offer crucial heart and kidney protection. Our improved understanding of immunometabolism and the microbiome has opened new biological areas for treatment. The future will focus on integration and personalization. The old one-size-fits-all method for metabolic disease no longer works. The next wave of treatments will likely involve tailored combination therapies based on detailed molecular profiling of each patient. An AI driven diagnostic tool might spot a patient with a "gut dysbiosis-driven" form of T2MD, leading to a personalized treatment plan that includes a GLP-1/GIP/glucagon tri-agonist and a specially designed live biotherapeutic to improve gut barrier function. Challenges certainly remain. Ensuring fair global access to these costly and complex new therapies is a significant societal and economic obstacle. We must also go further upstream and create better strategies for prevention. This includes addressing the unhealthy environment and the social factors that drive this pandemic. However, for the first time in modern medicine, we have the scientific and technological tools to not only manage metabolic diseases but also push them into remission and, in some cases, reverse the underlying issues. The path from understanding the metabolic chaos to controlling it will be the key medical challenge and opportunity of the next decade. Taken together, these developments highlight a paradigm shift from reductionist approaches toward integrated, systems-level management of metabolic disease.

6. Strengths and Limitations of Current Evidence

The current body of research on metabolic syndrome demonstrates several key strengths. First, large-scale clinical trials and mechanistic studies have consistently established insulin resistance, adipose dysfunction, and multi-organ crosstalk as central drivers of disease. Second, therapeutic advances-particularly incretin-based therapies and SGLT2 inhibitors-are supported by robust randomized controlled trials demonstrating significant metabolic, cardiovascular, and renal benefits. Additionally, emerging fields such as immunometabolism and multi-omics have expanded the conceptual framework of metabolic disease beyond traditional models.

However, important limitations remain. A substantial proportion of mechanistic insights are derived from preclinical or associative studies, limiting direct clinical translation. Evidence linking the gut microbiome to metabolic disease, while compelling, is heterogeneous and lacks standardized therapeutic approaches. Similarly, AI and precision medicine strategies, although promising, remain largely in early-stage or translational research with limited real-world validation. Furthermore, long-term safety, durability, and population-level applicability of newer pharmacological interventions require continued investigation. These gaps highlight the need for integrative, longitudinal, and clinically validated studies to fully realize the potential of current advances.

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Author Contributions

Shivangi Sharma: Data curation, Literature review, Writing-original draft, Visualization. Shivank Sharma: Conceptualization, Methodology, Supervision, Writing-review & editing, Validation, Project administration.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Generative AI Statement

The authors used ChatGPT as a language-assistance tool for grammar and phrasing improvement. They take full responsibility for all content.

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