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Review Article

Pathophysiological Interplay Between Cardiovascular Diseases and Metabolic Disorders: A Review of Shared Mechanisms and Emerging Therapeutic Approaches

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Abstract

Background and aims: Cardiovascular diseases (CVDs) and metabolic disorders, such as type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome, frequently coexist and contribute to a substantial global burden of morbidity and mortality. Accordingly, this review was designed to investigate the shared pathophysiological mechanisms underlying CVDs and metabolic disorders and to highlight emerging therapeutic strategies targeting these common pathways.

Methods: A structured narrative literature search was performed in PubMed, Scopus, and Web of Science, covering studies published between 2019 and 2025. Keywords related to inflammation, oxidative stress (OS), insulin resistance, endothelial dysfunction, gut microbiota, and cardiometabolic therapies were used for this purpose. Eligible peer-reviewed studies focusing on shared mechanisms or therapeutic implications underwent qualitative analysis.

Results: According to recent studies, low-grade inflammation, OS markers, impaired phosphoinositide 3-kinase/protein kinase B insulin signaling, and microbiota-derived metabolites, such as trimethylamine N-oxide (TMAO), are strongly associated with increased cardiometabolic risk. Moreover, clinical studies revealed that patients with T2DM have a 2–4-fold higher risk of CVD, while increased TMAO levels are linked to a 30–60% rise in adverse cardiovascular outcomes. Emerging therapies, including sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, anti-inflammatory agents, and microbiota-targeted interventions, demonstrated measurable reductions in cardiovascular events and improved metabolic control in high-risk patients.

Conclusion: Overall, CVDs and metabolic disorders share standard mechanisms that can be increasingly targeted with emerging therapies. Recognizing these pathways helps clinicians and policymakers adopt integrated management strategies, promote earlier intervention in high-risk individuals, and implement evidence-based treatments that address both conditions simultaneously.

Keywords: Cardiovascular diseases, Metabolic disorders, Shared mechanisms, Therapeutic approaches, Personalized medicine

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Introduction

Cardiovascular diseases (CVDs) and metabolic disorders, including diabetes, obesity, and metabolic syndrome, have had serious global health burdens in the 21st century.[1] More precisely, they are the leading causes of morbidity and mortality worldwide and impose a substantial economic burden on healthcare systems.[2,3] According to the reports of the World Health Organization (WHO), CVD-related deaths increased from 17.5 million in 2012 to 17.9 million in 2016, comprising 31% of all deaths (2016, 2017). Projections estimate this number will reach 22.2 million by 2030. In addition, heart attack and stroke were the leading causes of death among CVDs (WHO, 2016).[4] Similarly, the prevalence of metabolic disorders is extremely high, with approximately 2 billion adults classified as overweight or obese.[5] Standard underlying mechanisms of CVDs and metabolic disorders include chronic inflammation, oxidative stress (OS), insulin resistance, and endothelial dysfunction.[6] In recent years, significant advances have been made in elucidating the molecular and cellular mechanisms underlying the interplay between CVDs and these disorders.[6] Previous studies have revealed how the gut microbiota influences systemic inflammation and metabolic health, offering new insights into the gut-heart axis.[7,8]

Additionally, some studies have identified novel biomarkers and therapeutic targets (e.g., micro ribonucleic acids and epigenetic modifications) that may pave the way for personalized medicine approaches.[9,10] Despite these advancements, many questions remain unanswered, and there is a pressing need for further research in order to translate these findings into clinical practice.[11] Current treatment approaches often focus on managing individual risk factors, such as hypertension (HTN) or

hyperglycemia. However, there is growing recognition of the need for integrated strategies that address the underlying mechanisms shared by these conditions.[12]

Despite extensive research on cardiovascular and metabolic disorders, existing reviews address these conditions separately or focus on isolated pathways. However, a comprehensive and integrated synthesis of the shared molecular mechanisms, including inflammation, OS, insulin resistance, endothelial dysfunction, and gut microbiota dysbiosis, remains limited. Furthermore, recent therapeutic advancements targeting these interconnected pathways have not been thoroughly evaluated. This gap highlights the need for an updated, mechanistically focused review that unifies current knowledge and clarifies how these shared pathways can inform more effective clinical and public health strategies.

Materials and Methods

This review was conducted as a narrative synthesis of the current evidence on the shared pathophysiological mechanisms linking CVDs and metabolic disorders. A comprehensive literature search was performed in PubMed, Scopus, and Web of Science, including studies published from 2019 to 2025. The search strategy incorporated a combination of medical subject headings and free-text keywords, including "cardiovascular diseases," "metabolic disorders," "diabetes," "obesity," "metabolic syndrome," "inflammation," "oxidative stress," "insulin resistance," "endothelial dysfunction," "gut microbiota," "cardiometabolic mechanisms," and "therapeutic approaches," using Boolean operators, such as AND, OR, and NOT, to refine the results.

Studies were eligible for inclusion if they (1) were peer-reviewed original research articles, systematic reviews, meta-analyses, or narrative reviews, (2) were published in English, and (3) focused on mechanistic links or shared biological pathways between CVDs and metabolic disorders. It should be noted that both human studies and relevant animal model studies were considered when they provided mechanistic insights applicable to cardiometabolic interactions.

The exclusion criteria included (1) non-peer-reviewed publications (e.g., editorials, letters, and conference abstracts), (2) studies unrelated to the shared mechanisms of CVDs and metabolic disorders, (3) articles focusing solely on single-disease outcomes without addressing cardiometabolic interplay, and (4) publications lacking mechanistic, pathophysiological, or clinically relevant content.

Titles, abstracts, and full texts were screened to ensure relevance, and the final selection of studies was synthesized qualitatively. Considering that this is a narrative rather than a systematic review, no formal risk-of-bias assessment or quantitative meta-analysis was performed.

Shared Pathophysiological Mechanisms

CVDs and metabolic disorders (diabetes, obesity, and metabolic syndrome) are interconnected through shared pathophysiological mechanisms, and these mechanisms create a bidirectional relationship in which each condition exacerbates the progression of the other. Key pathways include chronic inflammation, OS, insulin resistance, endothelial dysfunction, and the emerging role of gut microbiota[6] (Table 1). Gaining insight into these shared mechanisms is essential for designing targeted therapeutic strategies that tackle the underlying causes of these interrelated disorders.

Chronic Inflammation

Chronic low-grade inflammation represents a core characteristic common to both CVDs and metabolic disorders.[30] In metabolic conditions such as obesity and diabetes, visceral fat is widely recognized as a metabolically active tissue with endocrine properties, releasing numerous pro-inflammatory substances that contribute to systemic inflammation. Among them, tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP) play pivotal roles in systemic inflammation promotion and metabolic dysregulation.[31] Research has demonstrated that inflammatory cytokines promote endothelial cell activation, thereby inducing elevated expression of key adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), facilitating leukocyte recruitment and vascular inflammation. These molecules enhance leukocyte adhesion and migration across the endothelium, ultimately contributing to vascular inflammation and impaired endothelial function.[32] Moreover, these enhanced adhesion and migration processes facilitate the recruitment of monocytes and T-cells into the arterial wall, where they differentiate into macrophages and foam cells, respectively. Cell accumulation in the arterial wall drives atherosclerotic plaque formation and destabilization, thereby increasing the risk of heart attack and stroke.[33]

On the other hand, in obesity, hypertrophied adipocytes become dysfunctional and release free fatty acids (FFAs) into the bloodstream. FFAs engage toll-like receptors (TLRs) on immune cells, thus prompting the secretion of further pro-inflammatory cytokines. This TLR-mediated cytokine release creates a vicious cycle of inflammation that exacerbates both metabolic and cardiovascular dysfunction (Figure 1).[34]

Visceral adiposity enhances lipolysis and increases FFA levels, further stimulating inflammation (IL-6 and TNF-α) via TLR activation on immune cells. These events contribute to endothelial activation, upregulation of adhesion molecules (VCAM-1 and ICAM-1), leukocyte recruitment, and differentiation into foam cells, ultimately leading to plaque formation and atherosclerosis. Similarly, IL-6 contributes to insulin resistance by inducing the suppressor of cytokine signaling 3, a protein that interferes with insulin signaling, and promoting hepatic gluconeogenesis, which elevates blood glucose levels.[35]

Table 1. A Summary of Human Study Findings on the Pathophysiological Interplay Between Cardiovascular Diseases and Metabolic Disorders

Pathophysiological Mechanism	Human Study Findings	Implications/Conclusions	References
Chronic inflammation	Elevated CRP, IL-6, and TNF-α in patients with CVD and type 2 diabetes (T2D)	Chronic inflammation contributes to atherosclerosis and insulin resistance.	13
Insulin resistance	Insulin resistance observed in patients with hypertension (HTN), coronary artery disease, and heart failure	Insulin resistance is a central mechanism linking metabolic and cardiovascular disorders.	14
Endothelial dysfunction	Reduced flow-mediated dilation and NO bioavailability in diabetic and cardiovascular patients	Endothelial dysfunction serves as an early marker for atherosclerosis.	15
Gut microbiota dysbiosis	Altered Firmicutes/Bacteroidetes ratio and elevated TMAO levels in patients with obesity, T2D, and CVD	Microbiota-derived metabolites like TMAO promote inflammation and atherogenesis.	16
Adipokine imbalance	Elevated leptin and reduced adiponectin in patients with CVD and metabolic syndrome	The dysregulation of adipokines exacerbates inflammation and endothelial dysfunction.	17
Sympathetic nervous system overactivity	Sympathetic overactivity observed in patients with obesity and HTN	Sympathetic overactivation accelerates both metabolic and cardiovascular damage.	18
Chronic hyperglycemia	Elevated blood glucose levels contribute to endothelial injury and arterial stiffening.	Chronic hyperglycemia accelerates cardiovascular complications in metabolic disorders.	19
Renin-angiotensin-aldosterone system (RAAS) activation	Increased RAAS activity in patients with metabolic syndrome and CVD	RAAS overactivity contributes to insulin resistance and vascular damage.	20
Visceral fat accumulation	Abdominal fat is linked to the increased risk of heart disease and metabolic disturbances.	Visceral adiposity induces inflammation and alters lipid metabolism.	21
Endothelial nitric oxide synthase (eNOS) dysfunction	Impaired eNOS function in patients with T2D and HTN	eNOS dysfunction accelerates vascular stiffness and endothelial injury.	22
Hypercoagulability	Increased fibrinogen and D-dimer levels in patients with CVD and metabolic disorders	Hypercoagulability increases thrombotic risk in metabolic and cardiovascular conditions.	23
Mitochondrial dysfunction	Reduced mitochondrial function in skeletal muscles and vasculature of patients with obesity and CVD	Mitochondrial dysfunction exacerbates metabolic and cardiovascular decline.	24
Chronic kidney disease (CKD) and CVD	CKD accelerates cardiovascular risk in patients with metabolic disorders.	Kidney dysfunction promotes vascular calcification and increases CVD risk.	25
Autonomic dysfunction	Reduced heart rate variability and increased sympathetic tone in CVD and metabolic disorder patients	Autonomic dysfunction is associated with poor prognosis in both conditions.	26
Leptin resistance	Increased leptin levels and resistance in obesity and diabetes contribute to vascular dysfunction.	Leptin resistance leads to inflammation, endothelial dysfunction, and cardiovascular risk.	27
Inflammatory cytokine release from adipose tissue	The overproduction of IL-6, TNF-α, and other pro-inflammatory cytokines from visceral fat in CVD and metabolic patients	Inflammatory cytokines contribute to systemic inflammation, insulin resistance, and vascular damage.	28
Endocrine disruptors	Exposure to endocrine-disrupting chemicals correlates with increased risk of both CVD and metabolic disorders.	Environmental factors exacerbate metabolic and cardiovascular risks through hormonal modulation.	29

Note. CRP: C-reactive protein; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-alpha; CVD: Cardiovascular disease; NO: Nitric oxide; TMAO: Trimethylamine N-oxide.

TNF-α impairs insulin signaling by inhibiting insulin receptor substrate 1 (IRS-1) and promotes lipolysis, thereby increasing FFAs, which exacerbate insulin resistance.[36]

Oxidative Stress

OS, a disturbance in the equilibrium between reactive oxygen species (ROS) production and antioxidant defenses, is a key pathophysiological process in both CVDs and metabolic disorders. Excessive ROS production damages cellular components, such as lipids, proteins, and deoxyribonucleic acid (DNA), contributing to the development and progression of both conditions.[37] Cells counteract OS by triggering a network of antioxidant responses, primarily arranged by the transcription factor nuclear factor erythroid 2- 2-related factor 2 (Nrf2).[38] In the absence of stress, Nrf2 remains inactive as it is bound by Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm, which promotes its continuous degradation via the proteasome pathway.[39] However, under OS conditions, the post-translational modifications of Keap1 impair its ability to sequester Nrf2 in the cytoplasm, thereby facilitating Nrf2 stabilization and nuclear translocation.[40] After translocating to the nucleus, Nrf2 binds to antioxidant response elements in the promoter regions of target genes, inducing the transcription of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase. Generally, these enzymes enhance the cell's ability to detoxify ROS and limit oxidative damage.[41] In metabolic disorders and CVDs, chronic OS can impair this pathway, leading to increased cellular damage and disease progression.[37] Therapeutic strategies often aim to enhance Nrf2 activity to bolster the antioxidant defense system, potentially mitigating the adverse effects of OS in these conditions.[42]

On the other hand, ROS activate kinases such as c-Jun N-terminal kinase (JNK) and IκB kinase (IKK), which phosphorylate IRS-1, thereby impairing its function. This ROS-induced impairment of IRS-1 reduces glucose uptake

in muscle and fat tissue, thereby elevating blood glucose and worsening metabolic dysfunction (Figure 2).[43]

Under physiological conditions, Nrf2 is sequestered in the cytoplasm by Keap1 and targeted for proteasomal degradation. The OS-induced modifications of Keap1 diminish its ability to sequester Nrf2, thereby enhancing Nrf2 stabilization and nuclear translocation, which, in turn, activate the transcription of antioxidant genes

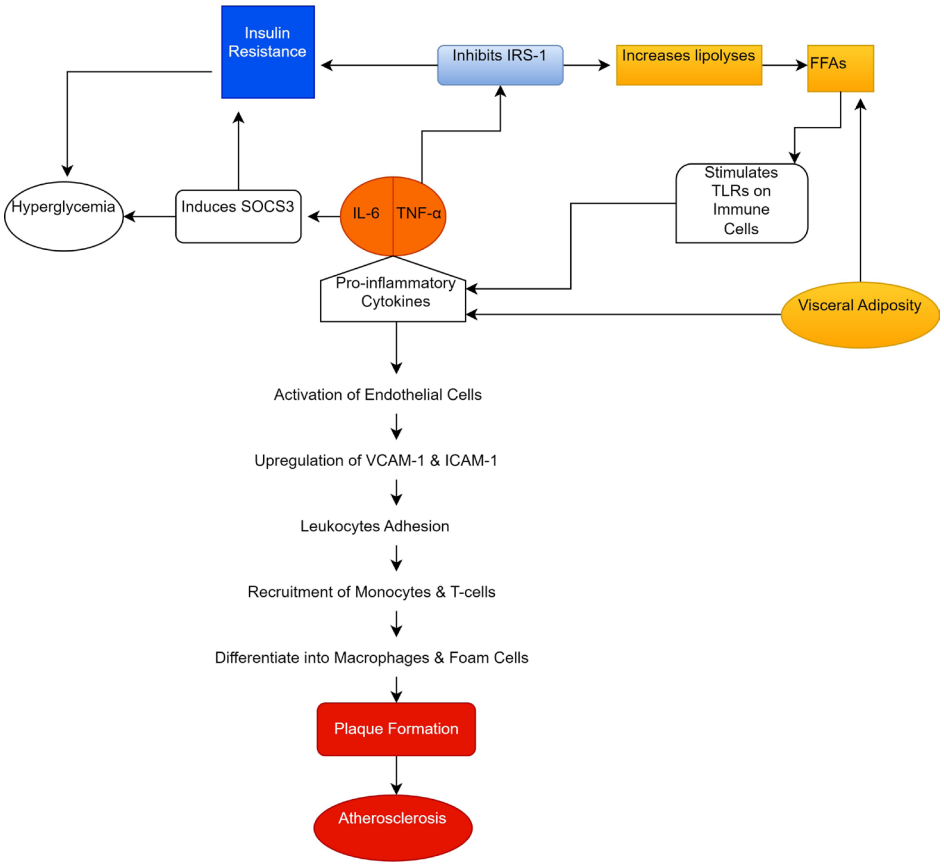

Figure 1. Pathophysiological Link Between Insulin Resistance, Visceral Adiposity, and Atherosclerosis
Note. SOCS3: Suppressor of cytokine signaling 3; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-alpha; IRS-1: Insulin receptor substrate 1; TLR: Toll-like receptor; FFA: Free fatty acid; VCAM-1: Vascular cell adhesion molecule-1; ICAM-1: Intercellular adhesion molecule-1

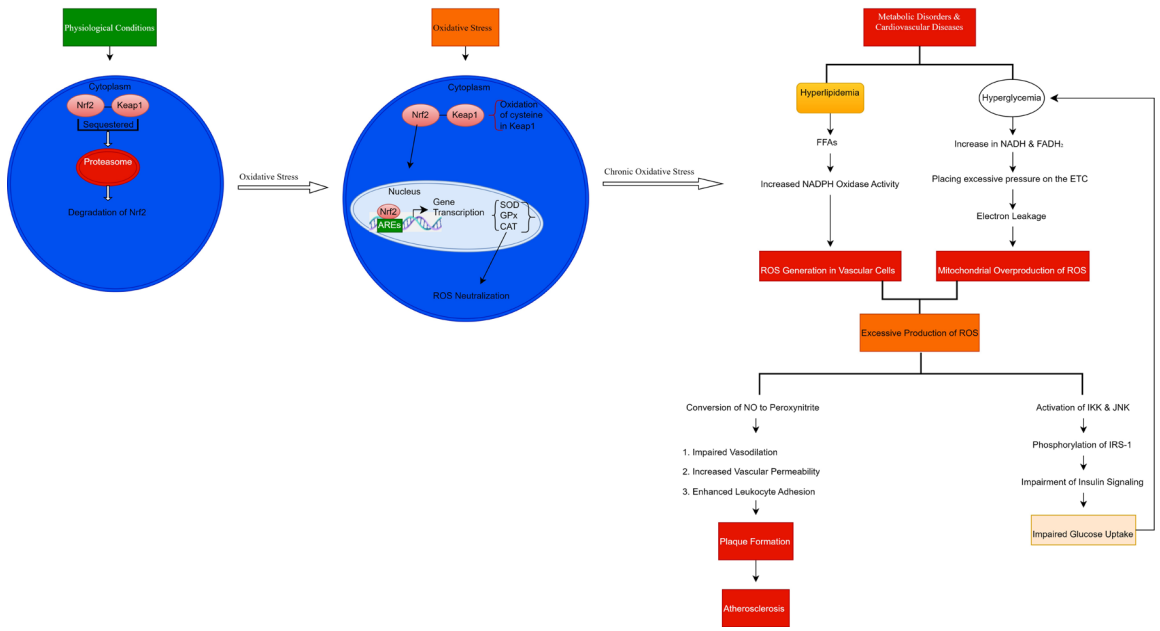

Figure 2. Role of Oxidative Stress and Nuclear Factor Erythroid 2-Related Factor 2 Signaling in the Development of Cardiometabolic Disorders
Note. ARE: Antioxidant response element; Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; ROS: Reactive oxygen species; CAT: Catalase; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; FFA: Free fatty acid; NADH: **Nicotinamide adenine dinucleotide**; FADH: Flavin adenine dinucleotide; ETC: Electron transport chain; NO: Nitric oxide; JNK: c-Jun N-terminal kinase; IKK: IκB kinase; IRS-1: Insulin receptor substrate 1

(*SOD*, *GPx*, and *CAT*) to counteract ROS. In chronic OS, metabolic disorders (e.g., hyperglycemia and hyperlipidemia) enhance mitochondrial ROS production and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, respectively. Excessive ROS leads to the conversion of nitric oxide (NO) to peroxynitrite, impaired vasodilation, increased vascular permeability, leukocyte adhesion, and plaque formation, ultimately promoting atherosclerosis. Simultaneously, ROS activate stress kinases (IKK and JNK), which impair insulin signaling and glucose uptake, leading to hyperglycemia and creating a vicious cycle.

Insulin Resistance

Insulin resistance, a hallmark of T2D and metabolic syndrome, is a key link between metabolic disorders and CVDs. It occurs when cells in tissues like muscle, liver, and fat become less responsive to insulin, impairing glucose uptake and metabolism. The insulin signaling pathway is central to this process.[44] Under normal conditions, insulin binds to its receptor (INSR), activating receptor tyrosine kinases that phosphorylate IRSs. This IRS phosphorylation activates the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, which is crucial for mediating the translocation of glucose transporter type 4 (GLUT4) to the cell membrane. As a result, glucose uptake by cells is significantly increased, supporting effective glucose utilization. Moreover, it inhibits hepatic gluconeogenesis and supports cell growth and survival.[45] This pathway is disrupted in insulin resistance.[46] Chronic inflammation, OS, and lipid accumulation (diacylglycerol and ceramides) activate stress kinases, such as JNK and IκB kinase beta.[47] These kinases phosphorylate IRS proteins on inhibitory sites, thereby reducing PI3K/Akt activation. As a result, GLUT4 translocation is impaired, glucose uptake decreases, and hepatic glucose production increases, leading to hyperglycemia.[48] In addition, hyperglycemia promotes the formation of advanced glycation end products, which cross-link with collagen and other proteins in the vascular wall, leading to increased stiffness and reduced compliance.[49] Furthermore, impaired insulin signaling alters lipid homeostasis by elevating triglyceride and low-density lipoprotein (LDL) cholesterol levels while concurrently decreasing high-density lipoprotein cholesterol, thereby fostering a lipid profile strongly associated with atherosclerotic risk.[50]

On the other hand, insulin resistance impairs endothelial function by reducing NO production while increasing endothelin-1 (ET-1) expression, a potent vasoconstrictor. This insulin-resistance-induced imbalance in NO and ET-1 leads to impaired vasodilation, increased vascular resistance, and HTN, further exacerbating cardiovascular risk (Figure 3).[51] It is noteworthy that therapeutic approaches often focus on improving insulin sensitivity

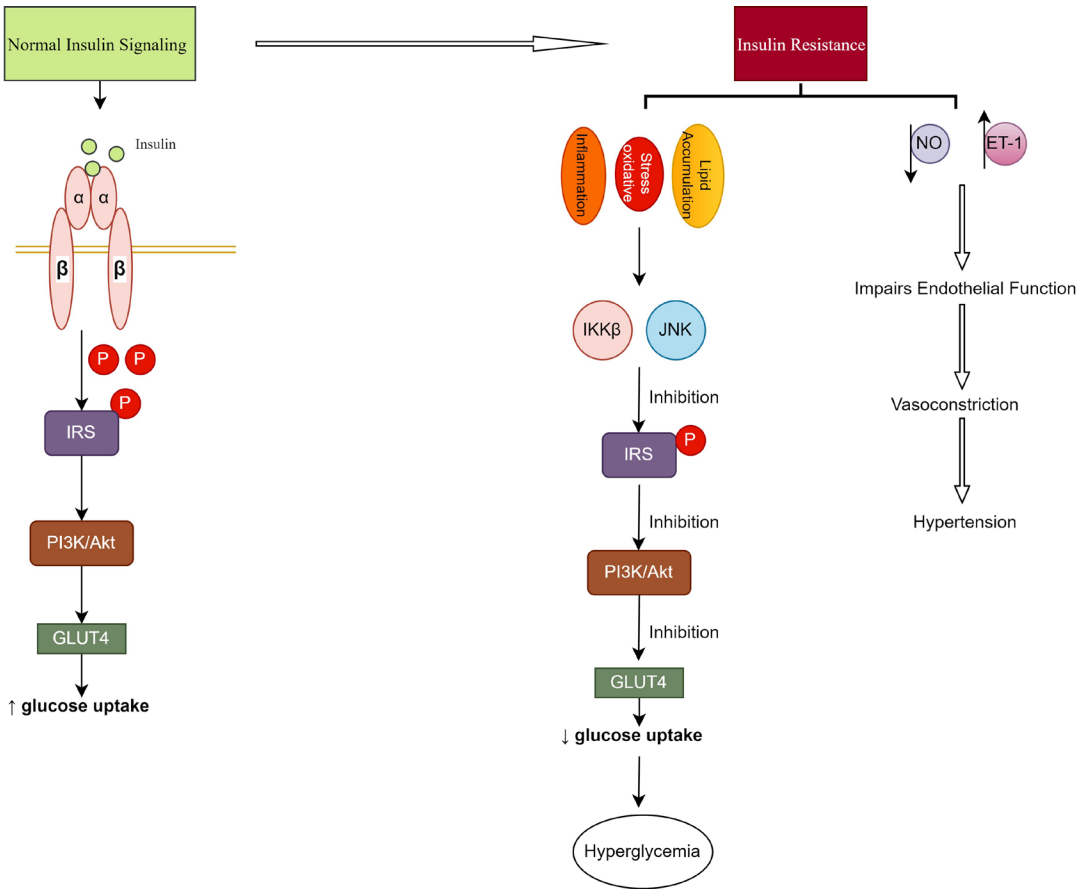

Figure 3. Schematic Representation of Normal Insulin Signaling Versus Insulin Resistance and Its Vascular Consequences
IRS: Insulin receptor substrate; GLUT4: Glucose transporter type 4; PI3K/Akt: Phosphoinositide 3-kinase/protein kinase B; NO: Nitric oxide; ET-1: Endothelin-1; IKKβ: IκB kinase beta; JNK: c-Jun N-terminal kinase

through lifestyle changes, medications (e.g., metformin), or targeting inflammatory pathways in order to restore proper insulin signaling.[52]

Under normal conditions, insulin binding to its receptor activates the IRS-PI3K/Akt pathway, leading to GLUT4 translocation and increased glucose uptake. Moreover, in insulin resistance, pro-inflammatory cytokines, OS, and lipid accumulation activate the IκB kinase beta and JNK pathways, inhibiting IRS function and downstream signaling, leading to reduced glucose uptake and hyperglycemia. Additionally, insulin resistance impairs endothelial function by decreasing NO while increasing ET-1, thereby promoting vasoconstriction and contributing to HTN.

Endothelial Dysfunction

The endothelium, a monolayer of cells that lines blood vessels, is essential for maintaining vascular homeostasis.[53] Endothelial dysfunction, marked by decreased NO bioavailability, heightened OS, and increased inflammation, is a pivotal early event in the pathogenesis of both CVDs and metabolic disorders. Furthermore, it augments the macrophage uptake of oxidized LDL, fostering foam cell formation and hastening plaque progression.[54] Under physiological conditions, endothelial NO synthase (eNOS) generates NO, which facilitates vasodilation, suppresses inflammation, and inhibits platelet aggregation.[55] Risk factors like hyperglycemia, OS, and inflammation reduce NO bioavailability in CVDs and metabolic diseases. This reduction in NO occurs due to eNOS uncoupling, in which eNOS produces superoxide rather than NO, as well as increased ROS-mediated scavenging of NO.[55] Excess ROS, generated by nicotinamide adenine dinucleotide phosphate oxidases and mitochondrial dysfunction, directly damages endothelial cells and reduces NO levels. ROS trigger pro-inflammatory signaling pathways, notably activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This activation enhances the expression of adhesion molecules, such as ICAM-1 and VCAM-1.[56] Moreover, chronic inflammation, driven by cytokines such as TNF-α and IL-6, disrupts endothelial function by activating NF-κB and other signaling pathways. In addition, this inflammation-induced activation leads to increased expression of adhesion molecules, chemokines, and endothelin-1, further impairing vascular homeostasis.[57] Additionally, endothelial dysfunction contributes to insulin resistance by impairing insulin delivery to skeletal muscle and adipose tissue.[58] Insulin resistance in endothelial cells reduces PI3K/Akt signaling, thereby diminishing eNOS activation and NO production.[59]

Gut Microbiota

Emerging evidence highlights the role of gut microbiota in the pathogenesis of both CVDs and metabolic disorders.[60,61] The gut microbiota, which encompasses a wide variety of microorganisms within the gastrointestinal tract, is essential for regulating host metabolic processes, controlling inflammation, and influencing immune responses.[62] Disruptions in its composition can initiate innate immune responses through key pathways involving TLRs and the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 inflammasome. This immunological activation leads to the increased secretion of pro-inflammatory cytokines, including TNF-α and IL-6, which play a critical role in the onset and progression of metabolic diseases and CVDs.[63,64] Further, the gut microbiota influences bile acid profiles, which, in turn, regulate lipid metabolism and glucose homeostasis by activating receptors such as the farnesoid X receptor and the Takeda G protein-coupled receptor 5.[65,66] Based on previous studies, dysbiosis alters bile acid composition, impairing these signaling pathways and contributing to metabolic disorders.[8,67] It is also linked to enhanced intestinal permeability, allowing bacterial endotoxins (e.g., lipopolysaccharide) to translocate into the bloodstream.[68] Furthermore, gut microbiota generate various metabolites, including short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, as well as trimethylamine N-oxide (TMAO) and bile acids.[69] SCFAs are acknowledged for their anti-inflammatory properties and advantageous effects on metabolic health.[70] In contrast, TMAO, produced from dietary nutrients (e.g., choline and carnitine), is associated with increased atherosclerotic and cardiovascular risk.[71] Dysbiosis alters the balance of these metabolites, thereby promoting inflammation and metabolic dysfunction.[72]

Clinical Implications and Therapeutic Approaches

The shared pathophysiological mechanisms between CVDs and metabolic disorders (diabetes, obesity, and metabolic syndrome) provide a foundation for developing integrated therapeutic strategies.[73] This section will explore the clinical implications of these shared mechanisms and discuss current and emerging therapeutic approaches, including lifestyle interventions, pharmacological therapies, personalized medicine, and future directions.

Lifestyle Interventions

Lifestyle modifications are the cornerstone of managing both CVDs and metabolic disorders. More precisely, these interventions not only address risk factors such as obesity, HTN, and dyslipidemia but also target underlying mechanisms, such as inflammation, OS, and insulin resistance.[74] The Mediterranean diet, characterized by a high intake of fruits, vegetables, whole grains, nuts, and olive oil, is renowned for its health benefits and has been shown to reduce inflammation, improve lipid profiles, and enhance insulin sensitivity.[75] According to some studies, diets emphasizing plant-based foods and minimizing animal products are associated with lower inflammation, improved endothelial function, and reduced cardiovascular risk.[8,76] Moreover, research has reported that in addition to a healthy diet, regular exercise

improves insulin sensitivity, reduces blood pressure, and enhances cardiovascular fitness.[77] Various forms of physical activity (e.g., aerobic exercise, resistance training, and high-intensity interval training) have demonstrated significant therapeutic benefits for individuals with CVDs and metabolic disorders. Likewise, exercise reduces visceral fat, a vital source of pro-inflammatory cytokines, thereby lowering systemic inflammation.[78,79] The findings of one study revealed that losing even a small amount of weight (about 5–10% of one's body weight) can lead to substantial improvements in metabolic health and reduce the risk of CVDs.[80]

Pharmacological Therapies

Pharmacological treatments targeting shared mechanisms between CVDs and metabolic disorders have shown promise in improving outcomes for patients with these conditions. These therapies include both established drugs and novel agents under investigation.[81]

Metformin, a standard first-line treatment for T2D, primarily acts by inhibiting hepatic gluconeogenesis, thereby reducing glucose production in the liver. Similarly, it improves insulin sensitivity in peripheral tissues, leading to better glucose uptake by muscle and adipose cells. Moreover, it activates adenosine monophosphate-activated protein kinase, a critical enzyme that regulates cellular energy balance, thereby further suppressing glucose production and promoting fatty acid oxidation.[82] In metabolic diseases, metformin helps lower blood glucose levels, improves lipid profiles, and may aid in weight management.[83] In CVDs, its benefits are attributed to improved metabolic control, reduced inflammation, and potential protective effects on endothelial function, which generally lower the risk of cardiovascular events. These mechanisms make metformin a cornerstone in the management of metabolic and cardiovascular conditions.[84]

Likewise, sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, function by inhibiting SGLT2 in the proximal tubules of the kidney, thereby reducing glucose reabsorption and increasing its excretion in the urine (glucosuria). This mechanism lowers blood glucose levels independently of insulin.[85] In metabolic diseases, SGLT2 inhibitors also improve glycemic control, reduce body weight, and lower blood pressure.[86] In CVDs, they provide significant benefits by reducing heart failure hospitalizations and alleviating cardiovascular outcomes.[87] These effects are attributed to their ability to promote natriuresis (sodium excretion), reduce fluid overload, improve cardiac energy metabolism, and potentially reduce inflammation and OS. These dual benefits make SGLT2 inhibitors valuable in managing both metabolic and cardiovascular conditions.[88]

Moreover, glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide and semaglutide, mimic the actions of the natural incretin hormone GLP-1. They help lower blood sugar by boosting glucose-dependent insulin secretion, suppressing glucagon release, and slowing gastric emptying, all of which contribute to lowering blood glucose levels.[89] In metabolic conditions, GLP-1 receptor agonists help regulate blood glucose levels, facilitate weight reduction, and decrease appetite.[90] In the context of CVDs, these receptor agonists have demonstrated the ability to lower the risk of major adverse cardiovascular events, including heart attacks and strokes. Additionally, they achieve this goal by enhancing endothelial function, reducing systemic inflammation, supporting weight loss, and controlling blood pressure. These multifaceted benefits make GLP-1 receptor agonists effective in managing both metabolic and cardiovascular conditions.[91]

Statins lower cholesterol by blocking 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is an essential liver enzyme in cholesterol production. This inhibition reduces LDL cholesterol (LDL-C) production but increases LDL particle clearance from the bloodstream. They also have anti-inflammatory effects, as evidenced by reductions in CRP levels. In addition, statins improve lipid profiles by lowering LDL-C, triglycerides, and total cholesterol while modestly increasing high-density lipoprotein cholesterol.[92] In CVDs, they considerably reduce the risk of atherosclerotic cardiovascular events (e.g., heart attack and stroke) by stabilizing atherosclerotic plaques, reducing inflammation, and improving endothelial function. These effects make statins the basis for preventing and managing cardiovascular and metabolic disorders.[93]

Drugs targeting specific inflammatory pathways, such as IL-1β inhibitors (canakinumab) and TNF-α inhibitors, are being investigated for their potential to reduce cardiovascular risk in patients with metabolic disorders.[94,95] Anti-inflammatory agents target and reduce chronic inflammation, a key driver in both metabolic disorders and CVDs. They function by inhibiting pro-inflammatory pathways (e.g., cytokines like IL-1β, IL-6, and TNF-α) or modulating immune responses. Furthermore, these agents improve insulin sensitivity, reduce hyperglycemia, and mitigate complications such as insulin resistance and fatty liver disease.[94,95] In CVDs, they also lower the risk of atherosclerosis and myocardial infarction by reducing vascular inflammation, stabilizing plaques, and improving endothelial function. By addressing the underlying inflammatory processes, anti-inflammatory agents also provide therapeutic benefits in the management of these interconnected conditions.[94,96]

Novel antioxidants, such as mitochondria-targeted agents (e.g., MitoQ), aim to reduce OS while improving endothelial function. These agents hold promise for treating both CVDs and metabolic disorders.[97] Antioxidants act by neutralizing ROS and reducing OS, a key contributor to cellular damage in metabolic disorders and CVDs. More precisely, they enhance the body's natural defense mechanisms by scavenging free radicals and protecting cells from oxidative damage. Moreover, antioxidants improve insulin sensitivity, reduce inflammation, and protect pancreatic beta cells, helping

to manage diabetes and its complications.[98] In CVDs, they also prevent oxidative damage to lipids, proteins, and DNA, reducing the progression of atherosclerosis, improving endothelial function, and lowering the risk of heart failure and myocardial infarction. By mitigating OS, antioxidants play a protective role in these conditions.[98]

Probiotics, prebiotics, and fecal transplants aim to restore gut microbiota balance and reduce inflammation. It should be noted that gut microbiota modulators influence the microbiome by promoting beneficial bacteria and suppressing harmful ones, thereby improving gut health and systemic outcomes.[99] This modulation influences metabolic and cardiovascular health through several mechanisms, including improved gut barrier function, reduced systemic inflammation, and enhanced production of metabolites (e.g., SCFAs). Moreover, these modulators improve insulin sensitivity, glucose metabolism, and lipid profiles while reducing obesity-related inflammation.[64] In CVDs, they help lower blood pressure, reduce atherosclerosis, and improve lipid metabolism by decreasing systemic inflammation and OS. By targeting the gut microbiome, these agents offer a novel approach to managing metabolic and cardiovascular conditions.[64]

Personalized Medicine

Personalized medicine in metabolic disorders and CVDs tailors treatment based on individual genetic, molecular, and clinical profiles. It uses biomarkers, genetic testing, and advanced diagnostics to predict disease risk, select optimal therapies, and monitor responses. Furthermore, it helps customize diabetes management by targeting specific pathways (e.g., insulin resistance and beta-cell dysfunction) and selecting drugs such as GLP-1 agonists or SGLT2 inhibitors based on patient profiles. Additionally, it guides the use of statins, antiplatelet therapies, or anti-inflammatory agents based on genetic predispositions (proprotein convertase subtilisin/kexin type 9 mutations) or biomarker levels (high-sensitivity CRP and LDL-C).[100,101] Biomarkers such as high-sensitivity CRP, TMAO, and micro ribonucleic acids can help identify patients at high risk for CVDs and metabolic complications. These biomarkers serve a dual purpose; they help inform clinical treatment decisions and are essential for evaluating how well a patient is responding to therapy.[102,103] Recent advancements in omics technologies (e.g., genomics, proteomics, and metabolomics) are accelerating the discovery of new biomarkers and potential therapeutic targets.[104]

On the other hand, genetic variants associated with insulin resistance, inflammation, and lipid metabolism can influence an individual's response to therapy.[105] Further, epigenetic changes (e.g., DNA methylation and histone modifications) affect gene expression involved in cardiovascular and metabolic diseases.[106] Targeting these modifications with epigenetic therapies is an area of active research. Based on research, personalized dietary recommendations informed by genetic and metabolic profiles can also optimize outcomes for patients with CVDs and metabolic disorders.[107] By focusing on individual variability, personalized medicine improves treatment efficacy, reduces side effects, and enhances outcomes in metabolic and cardiovascular care.[108]

Future Directions

The future of managing CVDs and metabolic disorders will leverage multi-target therapies and advanced technologies.[12] Combining SGLT2 inhibitors and GLP-1 receptor agonists provides dual glycemic control and cardiovascular protection.[109] In addition, nutraceuticals such as curcumin and resveratrol may improve outcomes through their anti-inflammatory and antioxidant properties.[110,111] Furthermore, artificial intelligence enhances risk prediction and treatment personalization through complex data analysis,[112] while mesenchymal stem cells hold potential for tissue repair.[113] Generally, a comprehensive public health strategy is crucial for addressing the global burden of these diseases.

Limitations of the Study

Despite the comprehensive exploration of shared pathophysiological mechanisms between CVDs and metabolic disorders, this review had several limitations. First, the scope was restricted to studies published in English, potentially excluding relevant data from non-English literature. Moreover, while efforts were made to include the most recent and high-quality evidence, the rapidly evolving nature of research in cardiovascular and metabolic fields indicates that some emerging findings may not be captured. Furthermore, heterogeneity among experimental models, clinical populations, and methodologies in the included studies may have limited the ability to draw definitive causal conclusions. Finally, although this review highlights potential therapeutic approaches, translating these strategies from preclinical studies to clinical practice remains a challenge. Accordingly, the long-term efficacy and safety of these strategies require further validation.

Conclusion

Cardiometabolic disorders stem from complex interactions among inflammatory, oxidative, metabolic, and endothelial pathways. Therefore, addressing these combined effects, rather than isolated risk factors, is crucial. Advances in therapeutics and biomarkers offer opportunities to identify risk precisely and target interventions. Nonetheless, further research is needed to translate mechanistic insights into scalable clinical and public health solutions. Eventually, linking molecular discoveries, patient data, and population-based prevention will improve strategies to combat the global burden of these diseases.

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