Metabolic Dysregulation in Cardiovascular Disease: Mechanisms and Therapeutic Targets

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Abstract

Metabolic dysregulation plays a pivotal role in the pathogenesis of cardiovascular disease (CVD), linking systemic metabolic disorders to cardiac dysfunction. Key mechanisms include insulin resistance, dyslipidemia, and chronic inflammation, contributing to endothelial dysfunction, atherosclerosis, and myocardial remodeling. Insulin resistance disrupts glucose and lipid metabolism, leading to elevated free fatty acids and triglycerides that promote vascular inflammation and plaque formation. Dyslipidemia exacerbates oxidative stress and endothelial injury, fostering atherogenesis. Chronic inflammation, driven by adipokines and cytokines from dysfunctional adipose tissue, further aggravates vascular and cardiac damage. Therapeutic targets are being explored to mitigate these metabolic disturbances, including agents that improve insulin sensitivity, modulate lipid profiles, and reduce inflammation. Novel strategies such as GLP-1 receptor agonists, SGLT2 inhibitors, and anti-inflammatory therapies hold promise in addressing the metabolic underpinnings of CVD, offering a multifaceted approach to treatment and prevention.

Keywords: Metabolic dysregulation, cardiovascular disease (CVD), Insulin resistance, Dyslipidemia, Chronic inflammation

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, posing a significant burden on healthcare systems. Recent advances in medical research have increasingly highlighted the critical role of metabolic dysregulation in the pathogenesis of CVD. Metabolic disorders, including insulin resistance, dyslipidemia, and chronic inflammation, are intimately linked with cardiovascular dysfunction. These metabolic disturbances contribute to key pathological processes such as endothelial dysfunction, atherosclerosis, and myocardial remodeling, ultimately exacerbating the progression of heart disease. This paper aims to elucidate the complex interplay between metabolic dysfunction and cardiovascular disease, exploring the underlying mechanisms and potential therapeutic targets that promise improving patient outcomes. By addressing these metabolic aspects, we can advance toward more comprehensive and effective treatments for CVD.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, posing a significant burden on healthcare systems [1]. Recent advances in medical research have increasingly highlighted the critical role of metabolic dysregulation in the pathogenesis of CVD. Metabolic disorders, including insulin resistance, dyslipidemia, and chronic inflammation, are

intimately linked with cardiovascular dysfunction. These metabolic disturbances contribute to key pathological processes such as endothelial dysfunction, and atherosclerosis. Insulin resistance, a hallmark of metabolic syndrome and type 2 diabetes, profoundly affects cardiovascular health. It disrupts normal glucose and lipid metabolism, leading to elevated levels of free fatty acids and triglycerides in the bloodstream. Dyslipidemia, characterized by abnormal lipid profiles such as elevated low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol, is another critical factor in metabolic dysregulation. Studies have shown that the Surf4 protein plays a crucial role in lipoprotein transport within the liver, and its functional deficiency may exacerbate elevated levels of cholesterol and triglycerides, thereby promoting the development of atherosclerosis[2]. Additionally, Wang et al. discovered that specific amino acid residues in the MT-loop of MT1-MMP are crucial for its ability to cleave the LDL receptor, potentially impacting LDL metabolism and the progression of atherosclerosis[3]. High LDL cholesterol levels promote cholesterol accumulation in arterial walls, forming plaques that narrow and harden the arteries, a process known as atherosclerosis[4]. Concurrently, low levels of HDL cholesterol impair the reverse transport of cholesterol from tissues back to the liver for excretion. The combination of these lipid abnormalities accelerates oxidative stress and inflammation, further injuring the endothelium and exacerbating cardiovascular disease.

Endoplasmic reticulum (ER) stress is increasingly recognized as a critical factor in the pathogenesis of cardiovascular diseases (CVD). The ER is responsible for the proper folding and processing of proteins, lipid synthesis, and calcium storage [5]. When cells experience conditions that disrupt ER function, such as oxidative stress, inflammation, or nutrient deprivation, an accumulation of unfolded or misfolded proteins occurs, leading to ER stress. This triggers the unfolded protein response (UPR), a cellular mechanism aimed at restoring ER homeostasis. However, chronic ER stress can lead to apoptosis and inflammation, contributing to the development and progression of CVD, including atherosclerosis, myocardial infarction, and heart failure. In atherosclerosis, ER stress is implicated in the formation and progression of plaques. Macrophages and endothelial cells within atherosclerotic lesions often exhibit signs of ER stress due to factors like oxidative stress, modified lipoproteins, and inflammatory cytokines [6]. The activation of UPR pathways in these cells can lead to apoptosis and the release of inflammatory cytokines, exacerbating plaque instability and promoting thrombosis. Additionally, ER stress-induced apoptosis of endothelial cells contributes to endothelial dysfunction, a precursor to atherosclerosis, further linking ER stress to vascular disease. Studies have shown that reducing ER stress in these cells can diminish atherosclerotic plaque formation, highlighting the therapeutic potential of targeting ER stress in CVD [7].

Figure 1, illustrates the complex relationship between endoplasmic reticulum (ER) stress and cardiovascular diseases (CVD). It begins with the induction of ER stress by various stressors, including oxidative stress, inflammation, and nutrient deprivation. These stressors lead to an accumulation of misfolded proteins, triggering the unfolded protein response (UPR). The UPR's dual role is depicted: initially aiming to restore ER homeostasis, but with chronic activation, it

results in cellular apoptosis and inflammation. The figure specifically highlights the impact of sustained ER stress on endothelial cells, promoting endothelial dysfunction and atherosclerosis, and on cardiomyocytes, contributing to myocardial infarction and heart failure [8]. Arrows trace the pathway from ER stress to these cardiovascular outcomes, emphasizing how chronic ER stress exacerbates plaque formation, destabilization, and cardiac remodeling. The diagram also suggests potential therapeutic interventions targeting ER stress to mitigate CVD progression.

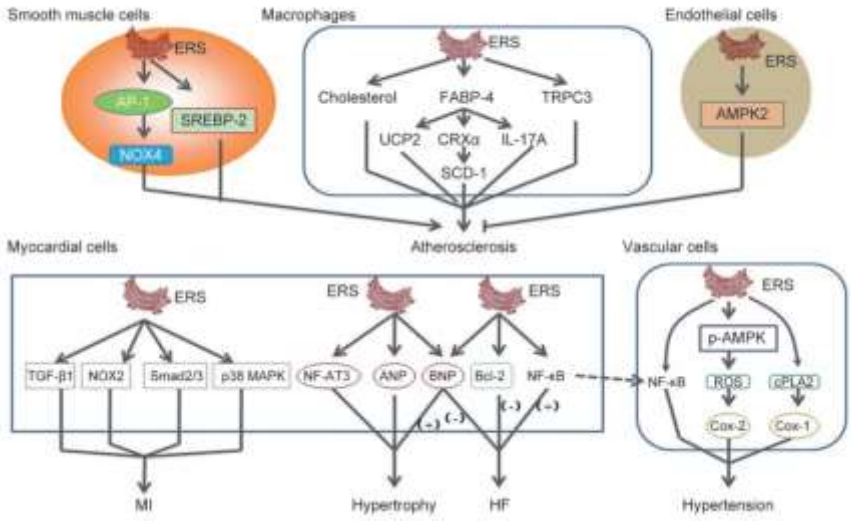

Figure 1: The relationship between endoplasmic reticulum stress and cardiovascular diseases.

ER stress also plays a significant role in myocardial infarction and heart failure. During ischemic events, such as myocardial infarction, the heart experiences a significant reduction in oxygen supply, leading to hypoxia and nutrient deprivation In the context of heart failure, chronic pressure overload and neurohormonal activation can sustain ER stress, exacerbating cardiac remodeling and dysfunction. Thus, therapeutic strategies aimed at mitigating ER stress, such as the use of chemical chaperones or modulators of UPR pathways, hold promise for improving outcomes in patients with cardiovascular diseases.

Chronic inflammation, often driven by adipokines and cytokines released from dysfunctional adipose tissue, is a pervasive feature of metabolic dysregulation in CVD. Inflammatory pathways perpetuate vascular injury and plaque instability, increasing the risk of acute cardiovascular events such as myocardial infarction and stroke [9]. The body's metabolism encompasses a complex network of biochemical pathways that govern the utilization and storage of nutrients, energy production, and waste elimination. Effective metabolic regulation maintains homeostasis, which is essential for the optimal functioning of cardiovascular tissues Proper regulation of lipid levels through diet, lifestyle, and pharmacological interventions is key to reducing cardiovascular risk. Thus, maintaining metabolic balance through healthy lifestyle choices, medical interventions, and targeted therapies is crucial for protecting the cardiovascular system from the detrimental effects of metabolic disturbances.

2. Mechanisms of Metabolic Dysregulation in Cardiovascular Disease (CVD)

Insulin resistance arises when the body's cells, particularly in muscle, fat, and liver tissues, become less responsive to the actions of insulin. This decreased sensitivity impairs the ability of insulin to promote glucose uptake and utilization in these tissues, leading to elevated blood glucose levels, a hallmark of type 2 diabetes. At the molecular level, insulin resistance is associated with defects in the insulin signaling pathway, including the insulin receptor and downstream signaling molecules such as insulin receptor substrate (IRS) proteins and phosphoinositide 3-kinase (PI3K). Chronic exposure to high levels of free fatty acids and inflammatory cytokines further exacerbates insulin resistance by interfering with these signaling pathways. This hyperglycemia stimulates further insulin secretion from the pancreas, leading to hyperinsulinemia, which in itself can have deleterious effects on the cardiovascular system [10].

Table 1, illustrates the pivotal role of endoplasmic reticulum (ER) stress in the pathogenesis of cardiovascular diseases, encompassing atherosclerosis, heart failure, hypertension, myocardial infarction, arrhythmias, and aortic aneurysm. At the core of this depiction lies the ER, a vital organelle regulating protein folding and calcium homeostasis within cells. Dysregulation of ER function triggers unfolded protein response pathways mediated by PERK, ATF6, and IRE1α, initiating a cascade of events implicated in cardiovascular pathology. In atherosclerosis, ER stress promotes endothelial dysfunction and inflammation, fostering plaque formation. In heart failure, ER stress-induced cardiomyocyte apoptosis exacerbates myocardial damage. Hypertension ensues from ER stress-mediated endothelial dysfunction and vascular remodeling. Myocardial infarction is worsened by ER stress, increasing infarct size and impairing cardiac function. Arrhythmias result from ER stress-induced ion channel alterations and disrupted calcium handling. Aortic aneurysm development involves ER stress-mediated vascular smooth muscle cell apoptosis and extracellular matrix degradation [11]. Therapeutically targeting ER stress pathways holds promise for ameliorating cardiovascular diseases, underscoring the significance of understanding ER stress mechanisms in clinical management.

Table 1: Endoplasmic reticulum stress is involved in the development of cardiovascular diseases

Cardiovascular Disease	Mechanism of ER Stress Involvement	Evidence
Atherosclerosis	ER stress promotes endothelial dysfunction and inflammation	- Activation of PERK and ATF6 pathways - Increased expression of CHOP
Heart Failure	ER stress-induced apoptosis of cardiomyocytes contributes	- Elevated ER stress markers in failing - Amelioration of heart failure with

Hypertension	ER stress-mediated endothelial dysfunction and vascular	- Activation of IRE1α and PERK pathways - Increased expression of ATF6
Myocardial Infarction	ER stress exacerbates ischemia-reperfusion injury,	- Activation of CHOP - PERK/eIF2α-mediated protein translation
Aortic Aneurysm	ER stress in vascular smooth muscle cells promotes apoptosis	- Activation of ATF6 and PERK pathways - MMP activation and collagen degradation

The inception of cardiovascular events often begins with endothelial dysfunction, a critical early step in the development of atherosclerosis. Endothelial cells, which line the inner surface of blood vessels, play a vital role in maintaining vascular homeostasis by regulating blood flow, vessel dilation, and preventing thrombosis. However, exposure to risk factors such as hyperlipidemia, hypertension, smoking, and diabetes induces oxidative stress and inflammation, impairing endothelial function. This dysfunction is characterized by a reduced bioavailability of nitric oxide (NO), a key vasodilator and anti-inflammatory molecule, leading to vasoconstriction, increased vascular permeability, and an upregulation of adhesion molecules. These changes promote the adhesion and transmigration of monocytes into the subendothelial space, where they differentiate into macrophages and ingest oxidized low-density lipoprotein (ox-LDL) to form foam cells, initiating fatty streak formation.

Figure 2, outlines the cellular events leading to the inception, progression, and manifestation of cardiovascular events. It begins with endothelial dysfunction, triggered by risk factors such as hyperlipidemia, hypertension, and smoking, leading to reduced nitric oxide (NO) bioavailability and increased oxidative stress[12]. The figure shows monocytes adhering to the dysfunctional endothelium, migrating into the subendothelial space, and transforming into macrophages that ingest oxidized LDL, forming foam cells. These foam cells accumulate, forming fatty streaks, and as the process continues, smooth muscle cells proliferate and secrete extracellular matrix, leading to mature plaque formation. Chronic inflammation within the plaque weakens the fibrous cap through matrix metalloproteinase activity, increasing the risk of rupture. Plaque rupture exposes thrombogenic material, causing thrombus formation, which can obstruct blood flow, resulting in myocardial infarction or stroke. Arrows indicate the sequential progression of these events, highlighting key cellular and molecular changes at each stage.

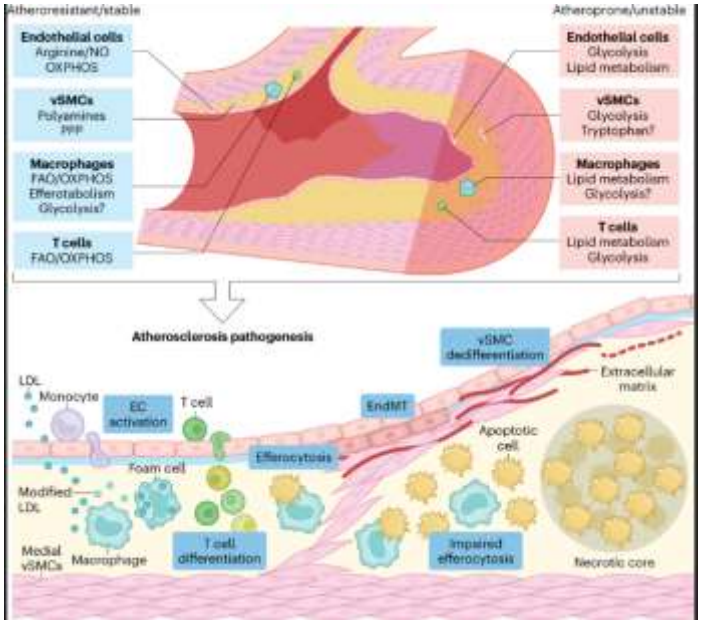

Figure 2: Cellular events leading to the inception, progression, and manifestation of cardiovascular events.

As atherosclerosis progresses, the continuous accumulation of foam cells, smooth muscle cells, and extracellular matrix components leads to the development of mature atherosclerotic plaques. Chronic inflammation within the plaque promotes further macrophage infiltration and the release of pro-inflammatory cytokines, perpetuating a cycle of inflammation and lipid accumulation. The plaque's fibrous cap, composed of smooth muscle cells and collagen, can become weakened due to enzymatic degradation by matrix metalloproteinases (MMPs) released by activated macrophages. This weakening increases the risk of plaque rupture, a critical event that manifests as an acute cardiovascular event. Plaque rupture exposes thrombogenic material to the bloodstream, leading to the rapid formation of a thrombus. If the thrombus significantly obstructs the coronary artery, it can result in myocardial infarction. Similarly, in cerebral arteries, it can lead to stroke. Thus, the progression from endothelial dysfunction to plaque formation and eventual rupture encapsulates the cellular events driving the manifestation of cardiovascular events.

Hyperinsulinemia, a compensatory response to insulin resistance, also exerts direct and indirect adverse effects on the cardiovascular system. Chronic high insulin levels can lead to increased sodium retention and sympathetic nervous system activation, both of which contribute to hypertension. Studies indicate that Surf4 deficiency can reduce intestinal lipid absorption and secretion, thereby affecting overall metabolism[13]. Insulin resistance contributes to cardiovascular disease through multiple interconnected pathways, including endothelial dysfunction, inflammation, hypertension, and dyslipidemia. These mechanisms collectively enhance the risk of atherosclerosis and its clinical sequelae, highlighting the importance of targeting insulin resistance in the prevention and management of cardiovascular disease.

Dyslipidemia is a metabolic disorder characterized by abnormal levels of lipids in the blood, including cholesterol and triglycerides. The primary types of dyslipidemia are

hypercholesterolemia (high levels of cholesterol), hypertriglyceridemia (high levels of triglycerides), mixed dyslipidemia (a combination of high cholesterol and triglycerides), and low levels of high-density lipoprotein (HDL) cholesterol [14]. Hypercholesterolemia, particularly elevated low-density lipoprotein (LDL) cholesterol, is a major risk factor for cardiovascular disease. As the process continues, smooth muscle cells migrate from the media to the intima layer of the artery, proliferate, and produce an extracellular matrix, which contributes to the growing plaque. This plaque can become calcified and fibrous, leading to the thickening and hardening of the arterial wall. Advanced plaques can rupture, causing thrombosis and acute cardiovascular events such as myocardial infarction and stroke. Dyslipidemia accelerates this process by continuously supplying the arterial wall with atherogenic lipoproteins, particularly small dense LDL particles, which are more susceptible to oxidation.

Chronic inflammation is a key player in the pathogenesis of cardiovascular disease (CVD), driving the development and progression of atherosclerosis [15]. The inflammatory process in CVD is complex and involves various pathways and mediators. Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), are produced by activated macrophages and other immune cells. In cardiac tissue, chronic inflammation contributes to myocardial remodeling and heart failure. Pro-inflammatory cytokines like TNF-α and IL-1β can induce cardiomyocyte apoptosis, fibrosis, and hypertrophy. This remodeling process impairs the structural integrity and function of the myocardium, leading to reduced cardiac output and the clinical manifestations of heart failure. In summary, chronic inflammation, mediated by a network of inflammatory pathways and adipokines, significantly contributes to vascular and cardiac damage in CVD. By understanding these mechanisms, we can develop targeted therapies to mitigate inflammation and its detrimental effects on cardiovascular health.

3. Pathophysiological Consequences of Metabolic Dysregulation

Endothelial dysfunction is a critical early event in the pathogenesis of cardiovascular disease (CVD) and serves as a pivotal link between metabolic dysregulation and vascular pathology. Several mechanisms contribute to endothelial dysfunction, particularly in the context of insulin resistance, dyslipidemia, and chronic inflammation. One of the primary mechanisms is the reduction in nitric oxide (NO) bioavailability. Insulin resistance impairs the insulin signaling pathways that facilitate NO production, leading to reduced vasodilation and increased vascular resistance. Additionally, elevated levels of reactive oxygen species (ROS) in states of metabolic dysregulation further degrade NO, compounding endothelial dysfunction. Markers of endothelial dysfunction include elevated levels of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which facilitate the adhesion and transmigration of leukocytes into the arterial wall. Other markers include increased endothelin-1, a potent vasoconstrictor, and decreased flow-mediated dilation (FMD), which measures the endothelium's ability to dilate in response to increased blood flow.

Endothelial dysfunction has profound implications for vascular health, setting the stage for atherosclerosis and other vascular diseases[16]. The reduced bioavailability of NO not only impairs vasodilation but also enhances platelet aggregation and adhesion, creating a pro-thrombotic environment. This pro-thrombotic state increases the risk of vascular occlusion and acute cardiovascular events such as myocardial infarction and stroke. The upregulation of adhesion molecules and increased endothelial permeability facilitate the infiltration of inflammatory cells and lipoproteins into the subendothelial space, promoting the formation of atherosclerotic plaques. These plaques, composed of lipids, inflammatory cells, and fibrous tissue, progressively narrow the arterial lumen and restrict blood flow. As the plaques mature, they can become unstable and prone to rupture, leading to the formation of occlusive thrombi. Endothelial dysfunction also promotes vascular inflammation and remodeling. The chronic inflammatory state associated with metabolic dysregulation leads to the release of cytokines and growth factors that stimulate the proliferation and migration of smooth muscle cells. These cells contribute to the thickening of the arterial wall and the development of intimal hyperplasia, further exacerbating the narrowing of blood vessels.

Atherosclerosis is a chronic inflammatory disease characterized by the buildup of plaques within the arterial walls. The process begins with endothelial dysfunction, which facilitates the entry of lipoproteins, particularly low-density lipoprotein (LDL), into the subendothelial space. Once inside, LDL particles undergo oxidation, triggering an inflammatory response. Monocytes are recruited to the site of inflammation, where they differentiate into macrophages and ingest oxidized LDL, forming foam cells. Foam cells accumulate to create fatty streaks, the earliest visible lesions of atherosclerosis. Over time, smooth muscle cells migrate from the media to the intima, proliferate, and produce extracellular matrix components, contributing to plaque growth and stability. As plaques enlarge, they can obstruct blood flow, leading to ischemic symptoms. Plaques can also become unstable and rupture, resulting in the formation of a thrombus that can occlude the artery and cause acute cardiovascular events. Oxidative stress plays a critical role in the development and progression of atherosclerosis. It occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. In metabolic dysregulation, elevated glucose and lipid levels increase ROS production, which promotes the oxidation of LDL particles. Oxidized LDL is more atherogenic, as it stimulates the expression of adhesion molecules, enhances monocyte recruitment, and promotes foam cell formation.

Oxidative stress plays a central role in the initiation and progression of atherosclerosis. It arises from an imbalance between the production of reactive oxygen species (ROS) and the body’s antioxidant defenses. Elevated glucose and lipid levels, common in metabolic dysregulation, increase ROS production. These reactive molecules oxidize LDL particles in the arterial wall, creating ox-LDL, which is highly atherogenic. Oxidative stress also damages endothelial cells, reducing the bioavailability of nitric oxide (NO), a critical molecule for maintaining vascular health. Reduced NO levels impair vasodilation and promote endothelial dysfunction. This chronic oxidative stress not only accelerates the formation of atherosclerotic plaques but also destabilizes

them by inducing the production of matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix of the fibrous cap. The weakened fibrous cap increases the risk of plaque rupture and subsequent thrombus formation, leading to acute cardiovascular events.

4. Clinical Implications and Future Directions

Metabolic management is increasingly recognized as a crucial component in the treatment of cardiovascular disease (CVD). Effective integration of metabolic strategies can address underlying metabolic dysregulation, such as insulin resistance and dyslipidemia, which are significant contributors to CVD. Interventions focusing on diet, exercise, and pharmacotherapy aim to optimize metabolic health, thereby improving cardiovascular outcomes. Personalized medicine holds great promise for the treatment of CVD by tailoring interventions based on individual metabolic profiles. Advances in genomic, transcriptomic, and metabolomic technologies enable precise characterization of an individual's metabolic state, facilitating the design of customized therapeutic strategies. Personalized metabolic management can optimize drug efficacy, minimize adverse effects, and address specific metabolic disturbances, offering a more effective approach to CVD treatment. For instance, genetic variations influencing lipid metabolism can guide the selection of lipid-lowering therapies, enhancing their effectiveness and reducing the risk of adverse cardiovascular events.

Future research should focus on elucidating the complex interactions between metabolic dysregulation and cardiovascular health and identifying novel metabolic biomarkers for early detection and risk stratification of CVD. Investigating the impact of emerging therapies targeting metabolic pathways, such as SGLT2 inhibitors and GLP-1 receptor agonists, on cardiovascular outcomes is essential. Additionally, exploring the role of the gut microbiome in metabolic health and its influence on cardiovascular disease could unveil new therapeutic targets. Integrating multi-omics data to develop comprehensive models of metabolic regulation in CVD will further enhance our understanding and treatment of this complex disease.

5. Conclusion

In conclusion, metabolic dysregulation is intricately linked to the pathogenesis and progression of cardiovascular disease (CVD), with insulin resistance, dyslipidemia, and chronic inflammation being key contributors. These metabolic disturbances foster endothelial dysfunction, atherosclerosis, and myocardial remodeling, exacerbating cardiovascular risk. Effective management of these metabolic abnormalities through lifestyle modifications, pharmacotherapy, and emerging therapies holds significant promise in mitigating CVD. Personalized medicine, leveraging genomic and metabolomic insights, can tailor interventions to individual metabolic profiles, optimizing treatment efficacy and reducing adverse outcomes. Future research should focus on unraveling the complex interactions between metabolic and cardiovascular health, identifying novel biomarkers, and exploring innovative therapeutic avenues, including the role of the gut microbiome. By advancing our understanding and targeting the metabolic underpinnings

of CVD, we can develop more comprehensive and effective strategies to improve patient outcomes and reduce the global burden of cardiovascular disease.

6. Conclusion

In conclusion, this paper sheds light on the intricate relationship between metabolic dysregulation and cardiovascular disease. Through a comprehensive analysis of various mechanisms, it becomes evident that metabolic dysfunction plays a crucial role in the development and progression of cardiovascular diseases. The paper highlights the importance of targeting metabolic pathways as potential therapeutic avenues to mitigate the impact of cardiovascular disease. By understanding the underlying mechanisms and identifying specific therapeutic targets, researchers and clinicians can strive towards developing innovative interventions to improve patient outcomes. The findings presented in this paper underscore the need for further research and collaboration to unravel the complexities of metabolic dysregulation in cardiovascular disease, ultimately leading to more effective treatment strategies and improved patient care.

Reference

[1] M. Aguilar-Ballester, G. Hurtado-Genovés, A. Taberner-Cortés, A. Herrero-Cervera, S. Martínez-Hervás, and H. González-Navarro, "Therapies for the treatment of cardiovascular disease associated with type 2 diabetes and dyslipidemia," *International Journal of Molecular Sciences,* vol. 22, no. 2, p. 660, 2021.

[2] Y. Shen, H.-M. Gu, S. Qin, and D.-W. Zhang, "Surf4, cargo trafficking, lipid metabolism, and therapeutic implications," *Journal of Molecular Cell Biology,* vol. 14, no. 9, p. mjac063, 2022.

[3] M. Wang *et al.*, "Identification of amino acid residues in the MT-loop of MT1-MMP critical for its ability to cleave low-density lipoprotein receptor," *Frontiers in Cardiovascular Medicine,* vol. 9, p. 917238, 2022.

[4] Y. Wu, S. Zhan, Y. Xu, and X. Gao, "RNA modifications in cardiovascular diseases, the potential therapeutic targets," *Life Sciences,* vol. 278, p. 119565, 2021.

[5] I. Akoumianakis, M. Polkinghorne, and C. Antoniades, "Non-canonical WNT signalling in cardiovascular disease: mechanisms and therapeutic implications," *Nature Reviews Cardiology,* vol. 19, no. 12, pp. 783-797, 2022.

[6] G. Lu *et al.*, "Autophagy in health and disease: From molecular mechanisms to therapeutic target," *MedComm,* vol. 3, no. 3, p. e150, 2022.

[7] M. Li, X. Chi, Y. Wang, S. Setrerrahmane, W. Xie, and H. Xu, "Trends in insulin resistance: insights into mechanisms and therapeutic strategy," *Signal transduction and targeted therapy,* vol. 7, no. 1, p. 216, 2022.

[8] J. Bozic *et al.*, "Role of adropin in cardiometabolic disorders: from pathophysiological mechanisms to therapeutic target," *Biomedicines,* vol. 9, no. 10, p. 1407, 2021.

[9] M.-W. Zhang, Y.-J. Shen, J. Shi, and J.-G. Yu, "MiR-223-3p in cardiovascular diseases: a biomarker and potential therapeutic target," *Frontiers in Cardiovascular Medicine,* vol. 7, p. 610561, 2021.

[10] J. D. Ravid, M. H. Kamel, and V. C. Chitalia, "Uraemic solutes as therapeutic targets in CKD-associated cardiovascular disease," *Nature Reviews Nephrology,* vol. 17, no. 6, pp. 402-416, 2021.

[11] A. A. Herrada, A. Olate-Briones, A. Rojas, C. Liu, N. Escobedo, and M. Piesche, "Adipose tissue macrophages as a therapeutic target in obesity-associated diseases," *Obesity Reviews,* vol. 22, no. 6, p. e13200, 2021.

[12] C. J. Ramachandra, S. Cong, X. Chan, E. P. Yap, F. Yu, and D. J. Hausenloy, "Oxidative stress in cardiac hypertrophy: From molecular mechanisms to novel therapeutic targets," *Free Radical Biology and Medicine,* vol. 166, pp. 297-312, 2021.

[13] G. Tao *et al.*, "Surf4 deficiency reduces intestinal lipid absorption and secretion and decreases metabolism in mice," *bioRxiv,* p. 2023.02. 08.527677, 2023.

[14] C. C. M. Correia, L. F. Rodrigues, B. R. de Avila Pelozin, E. M. Oliveira, and T. Fernandes, "Long non-coding RNAs in cardiovascular diseases: potential function as biomarkers and therapeutic targets of exercise training," *Non-coding RNA,* vol. 7, no. 4, p. 65, 2021.

[15] L. Wu, L. Wang, Y. Du, Y. Zhang, and J. Ren, "Mitochondrial quality control mechanisms as therapeutic targets in doxorubicin-induced cardiotoxicity," *Trends in Pharmacological Sciences,* vol. 44, no. 1, pp. 34-49, 2023.

[16] Y. Li *et al.*, "Diabetic vascular diseases: molecular mechanisms and therapeutic strategies," *Signal transduction and targeted therapy,* vol. 8, no. 1, p. 152, 2023.