Research Advances in Coronary Microvascular Dysfunction and Metabolic Syndrome: Postprint

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Abstract

In recent years, coronary microvascular dysfunction (CMD) and metabolic syndrome (MetS) have attracted considerable attention due to their adverse cardiovascular effects. CMD is a potential factor leading to myocardial ischemia and is closely associated with the onset, progression, and poor prognosis of cardiovascular disease. MetS is a group of metabolic disorders caused by the combined effects of genetic and environmental factors. There exists a certain association between CMD and MetS, and understanding the complex interactions between the two diseases is crucial for developing effective prevention and treatment strategies. This article aims to review the developmental history of both conditions, the relationship between various components of MetS and CMD, disease diagnosis and treatment, and future research directions, in order to provide reference for clinical practice.

Full Text

Advances in Coronary Microvascular Dysfunction and Metabolic Syndrome

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Abstract

Coronary microvascular dysfunction (CMD) and metabolic syndrome (MetS) have attracted considerable attention in recent years due to their adverse effects on the cardiovascular system. CMD is a potential factor leading to myocardial ischemia, closely associated with the onset, progression, and poor prognosis of cardiovascular diseases. MetS is a cluster of metabolic disorders resulting from the combined influence of genetic and environmental factors. There exists a significant association between CMD and MetS, and understanding the complex interactions between these two conditions is essential for developing effective prevention and treatment strategies. This article aims to review the developmental history of both diseases, the relationship between individual components of MetS and CMD, current diagnostic and therapeutic approaches, and future research directions, with the goal of providing valuable insights for clinical practice.

Keywords: Coronary heart disease; Coronary microvascular dysfunction; Metabolic syndrome; Review; Editorial

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Coronary microvascular dysfunction (CMD) refers to impaired coronary microcirculatory blood flow caused by structural and/or functional abnormalities of coronary microvessels, ultimately leading to myocardial ischemia. Diabetes, obesity, hypertension, and other risk factors promote the development and progression of CMD. As one of the primary mechanisms of ischemic heart disease, CMD is closely associated with adverse cardiovascular outcomes, yet its clinical diagnosis and treatment rates remain suboptimal. Research indicates that CMD occurs in approximately 40% to 64% of patients with myocardial ischemia, but only about 6.3% receive proper diagnosis and treatment. Metabolic syndrome (MetS) is a clinical syndrome characterized by the clustering of obesity, hyperglycemia, hypertension, and dyslipidemia that significantly impacts health. According to a report from the Chinese Center for Disease Control and Prevention, the prevalence of MetS among Chinese adults is 33.9%, affecting an estimated 450 million adults. Individuals with MetS face a threefold increased risk of cardiovascular and cerebrovascular disease and substantially higher premature mortality, representing a critical public health concern.

CMD and MetS are interrelated, with MetS serving as an important risk factor for CMD that can affect microvascular structure and function through multiple mechanisms. CMD and the various components of MetS often coexist and interact in complex ways, creating a vicious cycle of disease progression. Understanding these interactions is crucial for developing effective prevention and treatment strategies. This article provides a comprehensive overview of the current understanding of CMD and MetS, focusing on their developmental history, underlying mechanisms, therapeutic approaches, and future research directions to establish a theoretical foundation for more effective diagnosis and treatment.

1.1 Developmental History of CMD

In 1967, Likoff et al. first reported cases of typical angina symptoms with positive exercise treadmill tests despite normal coronary angiography, laying the initial conceptual groundwork for coronary microvascular disease. In 1973, Kemp et al. identified patients with exertional angina and normal coronary angiograms, formally naming the condition "cardiac syndrome X." Subsequently, the European Society of Cardiology included cardiac syndrome X in its 1997 guidelines for stable angina, prompting extensive research into CMD as the potential underlying mechanism. In the early 21st century, endothelial dysfunction was recognized as the primary pathogenic mechanism of CMD. Researchers later discovered that while percutaneous coronary intervention restored distal coronary pressure, it could reduce microcirculatory resistance during maximal hyperemia and induce microvascular remodeling, drawing increased attention to structural microvascular abnormalities. In 2007, Camici et al. proposed the concept of "microvascular dysfunction" and classified CMD into four types based on clinical context for the first time. During this period, CMD was recognized as an independent disease entity resulting from multiple pathogenic mechanisms. As epidemiological research progressed, accumulating evidence demonstrated that traditional cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia also played critical roles in CMD development. Research in CMD continued to advance, and in 2013, the European Society of Cardiology formally recognized CMD as a mechanism of myocardial ischemia, marking a new era in CMD research. Diagnostic criteria and treatment methods for CMD became hot topics in the field, with ongoing investigation into risk factors.

1.2 Developmental History of MetS

Since the 1980s, the concept of MetS has continuously evolved. Initially focused on single indicators such as blood pressure and glucose levels, the definition gradually expanded to include multiple physiological and biochemical parameters, garnering widespread research attention. In 1988, Reaven et al. first proposed the concept of "Syndrome X" to describe a cluster of cardiovascular risk factors associated with insulin resistance. In 1997, researchers identified insulin resistance as the pathophysiological basis for multiple metabolic disorders, causing disturbances in glucose and lipid metabolism collectively termed MetS. Although MetS gradually gained academic acceptance, its etiology and diagnosis remained controversial. In 1998, the World Health Organization formally defined MetS and established diagnostic criteria, providing a relatively uniform foundation for international research collaboration and data comparison. In 2001, the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) defined MetS as the presence of three or more of the following factors: abdominal obesity, dyslipidemia, hypertension, and insulin resistance. Subsequently, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) redefined MetS as three or more risk factors: central obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose. In 2005, the International Diabetes Federation (IDF) attempted to reconcile different clinical definitions by abandoning the WHO requirement for insulin resistance but making abdominal obesity a required component among five diagnostic factors. In

2009, IDF, NHLBI, AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity issued a joint statement proposing a "unified" definition of MetS. The joint statement specified that MetS could be diagnosed when any three of five risk factors were present: abdominal obesity, elevated blood pressure, elevated triglycerides, reduced high-density lipoprotein cholesterol, and elevated fasting glucose—a definition widely adopted in practice.

1.3 Development of Research on the Association Between CMD and MetS

Early research in the 1960s and 1970s focused on the relationship between obesity and cardiovascular disease, revealing associations between metabolic factors and cardiovascular disease development. The discovery of insulin resistance in the 1980s further solidified the link between metabolic factors and cardiovascular disease, with studies showing that insulin resistance correlated with increased cardiovascular risk and could contribute to disease development. During this same period, the concept of MetS was proposed, and researchers began investigating the role of microvascular dysfunction in cardiovascular disease pathogenesis. In the early 21st century, animal models provided substantial evidence that microvascular structural and functional abnormalities played key roles in the pathophysiology of cardiometabolic disease. CMD gained recognition as an independent disease entity while MetS diagnostic criteria gradually matured. Subsequent research explored the relationship between individual MetS components and CMD. Some investigators proposed that obesity causes CMD, which in turn may increase peripheral vascular resistance and reduce insulin-mediated glucose utilization, thereby contributing to hypertension and insulin resistance. This suggested that obesity might be a primary cause of CMD, while CMD could represent a potential pathogenic mechanism for hypertension and insulin resistance. Additional studies explored potential mechanisms through which MetS leads to CMD, though the temporal relationship between the two conditions remains unresolved.

2.1 Obesity and CMD

Obesity, characterized by excessive fat accumulation resulting from multiple factors and often accompanied by metabolic dysfunction in visceral organs, represents a major international public health concern. Obesity is closely associated with CMD; among patients with non-obstructive coronary artery disease, approximately 43.2% of non-central obese patients and 53.7% of centrally obese patients have CMD. Adipose tissue secretes numerous pro-inflammatory cytokines, including interleukin-6 (IL-6), CXC chemokine ligands, and tumor necrosis factor (TNF), which cause oxidative stress and inflammatory responses that damage endothelial cells. Leptin and adiponectin are two important proteins produced by adipocytes. Leptin stimulates fatty acid translocase translocation to the cell membrane by activating protein kinase A in endothelial cells, increasing fatty acid uptake and leading to oxidative stress and inflammation. Leptin also promotes inflammatory responses by stimulating release of TNF-α and IL-6, exacerbating endothelial dysfunction. Adiponectin enhances insulin sensitivity, reduces adhesion molecule expression on endothelium, inhibits macrophage transformation into foam cells, and decreases smooth muscle cell proliferation. However, adiponectin production and activity are reduced in obese individuals, diminishing its protective effects on endothelial cells.

Coronary perivascular adipose tissue (CPVAT) represents a potential mechanism in CMD pathogenesis. CPVAT is a type of visceral adipose tissue primarily surrounding epicardial coronary arteries. In obese patients, excessive adipose tissue accumulation leads to corresponding CPVAT increases. CPVAT-derived adipokines and vasoactive substances can directly affect coronary smooth muscle and endothelial cells, influencing vascular tone and blood flow. Excessive CPVAT accumulation increases intravascular pressure, causes arterial wall roughening, and promotes atherosclerotic plaque formation. These plaques can obstruct coronary arteries, reduce myocardial blood flow, and cause myocardial ischemia. Obesity, hypertension, and diabetes can disrupt the balance of CPVAT-derived vasoactive products, promote inflammatory cell infiltration, trigger coronary vascular smooth muscle and endothelial cell dysfunction, promote large artery stiffening, and cause downstream microvascular dysfunction.

2.2 Type 2 Diabetes Mellitus (T2DM) and CMD

T2DM is a common metabolic disorder characterized by insufficient insulin secretion and/or reduced tissue insulin sensitivity, leading to elevated blood glucose levels. T2DM is closely linked to various chronic metabolic diseases, including obesity, hypertension, and hypercholesterolemia. Recent clinical practice has revealed a strong relationship between T2DM and CMD, though the precise pathogenic mechanisms remain incompletely understood. Insulin resistance, a core mechanism of MetS, also represents the key link between CMD and T2DM. Insulin resistance leads to elevated insulin levels, reduced myocardial insulin responsiveness and glucose uptake, and increased risk of myocardial ischemia and hypoxia. Insulin resistance causes excessive fatty acid accumulation, increased free radical generation, and impaired endothelial and smooth muscle cell function. Hyperinsulinemia indirectly promotes endothelial dysfunction and accelerates CMD progression by activating inflammatory responses and upregulating pro-inflammatory cytokines. Additionally, hyperglycemia directly induces endothelial dysfunction by activating multiple cellular signaling pathways involved in apoptosis, proliferation, and senescence, leading to abnormal vasomotor function and exacerbating CMD. Some researchers have proposed that CMD may precede hyperglycemia in the course of T2DM development, but regardless of their temporal relationship, hyperglycemia adversely affects microcirculation.

2.3 Hypertension and CMD

Hypertension is an important risk factor for CMD, with pathological mechanisms involving several aspects. Chronic hypertension promotes left ventricular remodeling, including left ventricular wall thickening, cavity enlargement, and left atrial dilation. These changes increase myocardial oxygen consumption and reduce diastolic perfusion time and volume, creating a state of relative hypoxia. Hypertension also affects the structure and function of intramural coronary arteries (IMA), which connect major epicardial branches to smaller deep branches and play a crucial role in regulating myocardial perfusion. Under normal conditions, IMA exhibits strong vasodilatory capacity and is sensitive to shear stress, dilating during low perfusion states to ensure adequate oxygen supply to deep branches. However, in hypertensive patients, IMA often develops medial thickening, leading to luminal narrowing and impaired diastolic function that compromises its regulatory role. Furthermore, hypertension increases cardiac workload, causing accumulation of myocardial metabolic products, oxidative stress, inflammatory responses, endothelial dysfunction, and reduced synthesis of endothelium-derived hyperpolarizing factors, all contributing to CMD. Due to sympathetic overactivation and central nervous system dysfunction, hypertensive patients exhibit significantly elevated heart rate and cardiac output, potentially causing myocardial blood supply-demand imbalance. While researchers previously considered microvascular functional and structural impairment as consequences of hypertension, recent evidence suggests that microvascular changes, such as capillary rarefaction, may precede the development of hypertension. The coronary microcirculation represents the primary resistance vascular bed, and capillary density reduction caused by multiple risk factors increases peripheral vascular resistance. Sustained high peripheral resistance can lead to hypertension, which subsequently alters wall stress and induces adverse remodeling of intramural coronary arteries, ultimately causing resistance vessel remodeling.

2.4 Dyslipidemia and CMD

The European Society of Cardiology' s 2020 position statement on CMD evaluation and treatment emphasized the important role of dyslipidemia in CMD development. Clinical practice has shown that hypercholesterolemic patients exhibit significantly reduced coronary flow reserve, and plasma total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels correlate negatively with fractional flow reserve and microcirculatory resistance index. Hypercholesterolemia impairs microvascular function in acute coronary syndrome patients, increasing infarct size and promoting adverse cardiac remodeling after myocardial infarction. In patients with ST-segment elevation myocardial infarction, LDL-C is an independent predictor of CMD. Hypercholesterolemia triggers inflammatory responses within the microcirculation, primarily manifested as endothelial and platelet activation, leukocyte recruitment, and adhesion. Activated platelets attract leukocytes to lesion sites, which can subsequently obstruct capillary networks and reduce capillary perfusion. Additionally, reactions between phospholipids in hypercholesterolemia can generate oxidized low-density lipoprotein (oxLDL) or oxidized phospholipids (OxPL). OxPL can interact with cell membrane receptors, accumulate within cell membranes, and disrupt normal cellular function by reducing nitric oxide bioavailability, triggering immune responses that ultimately lead to atherosclerosis. OxPL can directly affect endothelial cells by interacting with lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) in endothelial cells. LOX-1 expression is induced by various inflammatory cytokines, oxidative stress, hemodynamic changes, and large amounts of oxLDL. In addition to oxLDL, LOX-1 can bind advanced glycation end products, activated platelets, and leukocytes, thereby promoting inflammatory and oxidative processes. Finally, interaction with oxPL causes further injury, subsequently activating endothelial cells and platelets and releasing various adhesion and pro-inflammatory cytokines, leading to monocyte recruitment, macrophage differentiation, foam cell formation, and excessive production of reactive oxygen species and inflammatory mediators that further damage the circulatory system. Moreover, hypercholesterolemia can affect microcirculation by damaging pericytes, which are essential components of capillaries that regulate blood flow and permeability. Studies have shown that pericytes are sensitive to pathological stimuli such as hypercholesterolemia and hyperglycemia, detaching from endothelial cells and leading to endothelial activation and apoptosis. This reduces capillary surface area and perfusion, causing capillary rarefaction.

3 Treatment and Management of CMD and MetS

Comprehensive management and treatment of CMD and MetS is a complex issue requiring personalized and integrated consideration of disease status, lifestyle, and pharmacological efficacy. Overall treatment approaches include health behavior interventions, pharmacological interventions, and other therapeutic modalities.

3.1 Health Behavior Interventions Health behavior interventions represent a crucial component of CMD and MetS management and form the foundation for all subsequent treatment strategies. The 2020 European Society of Cardiology position statement emphasized that lifestyle modification and risk factor management should be considered essential components of all treatment plans for patients with traditional cardiovascular risk factors, with or without signs of coronary atherosclerosis. Both domestic and international expert consensus guidelines for MetS explicitly recommend interventions including weight control, dietary modification, exercise, smoking cessation, alcohol limitation, sleep management, and stress management to improve metabolic abnormalities and maintain cardiovascular health.

3.1.1 Dietary Modification Dietary adjustment is an important therapeutic approach for CMD and MetS. Appropriate dietary modifications can control body weight, improve metabolic disturbances, and prevent cardiovascular events. The general principles include controlling total energy intake, reducing fat and cholesterol consumption, increasing dietary fiber and protein intake, and avoiding high-sugar, high-fat diets and excessive alcohol consumption. Specific dietary patterns such as the Mediterranean diet—characterized by plant-based foods rich in monounsaturated fatty acids and antioxidants with low animal fat and cholesterol—have been confirmed by multiple studies to effectively prevent MetS. A meta-analysis of 50 clinical studies including 534,906 patients demonstrated that adherence to the Mediterranean diet reduced MetS prevalence by 50% compared to non-adherent patients. Additional evidence indicates that the Mediterranean diet significantly reduces cardiovascular disease incidence beyond its effects on MetS.

3.1.2 Exercise Exercise is a vital component of CMD and MetS treatment. As a non-pharmacological intervention, regular physical activity increases energy expenditure, reduces body weight, improves lipid metabolism, lowers blood pressure, and enhances insulin sensitivity to prevent cardiovascular events. Aerobic exercise represents the optimal exercise modality for improving cardiovascular risk factors in adult MetS patients, offering clear advantages in improving glycemic and lipid profiles and effectively reducing cardiovascular disease risk. Traditional Chinese exercise practices such as Baduanjin, Wuqinxi, and Tai Chi have demonstrated significant auxiliary therapeutic effects in improving patient symptoms, reducing myocardial remodeling, promoting microvascular neogenesis and coronary collateral circulation establishment, improving survival rates, and reducing mortality.

3.1.3 Weight Control Weight control is an important therapeutic target for CMD and MetS. Overweight and obesity are major risk factors, and weight reduction can effectively improve patient outcomes and reduce cardiovascular events. Weight control is typically achieved through dietary modification and exercise. A reasonable dietary structure can effectively help patients lose weight and improve glucose and lipid metabolism. Moderate aerobic exercise increases energy expenditure, promotes fat breakdown and glycogen storage, and improves insulin sensitivity. Exercise also enhances cardiopulmonary function and improves exercise tolerance and quality of life.

3.1.4 Other Interventions Sleep and stress management are also important components of comprehensive CMD and MetS management. Chronic sleep deprivation and prolonged stress can lead to chronic inflammatory responses and metabolic abnormalities. Studies have shown that psychological interventions, cognitive behavioral therapy, relaxation training, and meditation can effectively improve sleep and mental health status and positively impact metabolic and cardiovascular health.

3.2 Medical Management of CMD and MetS While health behavior interventions help reduce CMD and MetS risk, pharmacological therapy plays a critical role in improving metabolic abnormalities and preventing cardiovascular events. For MetS patients, pharmacological treatment can effectively control blood glucose, lipids, and blood pressure to reduce cardiovascular events. Current medications for MetS primarily target individual components, including hypoglycemic agents, lipid-lowering drugs, and antihypertensive medications. The management goals for microvascular disease are to improve myocardial ischemia, correct underlying causes, enhance quality of life, and improve prognosis. Beta-blockers and short-acting nitrates are commonly used as first-line agents for CMD symptom control. Calcium channel blockers demonstrate good efficacy for chest pain caused by microvascular spasm but have limited effects on improving coronary blood flow. The 2019 European Society of Cardiology guidelines recommend beta-blockers, angiotensin-converting enzyme inhibitors, and statins for patients with coronary flow reserve (CFR) <2.0 or microcirculatory resistance index (IMR) >25 and negative acetylcholine provocation testing. In addition to these classic medications, many novel anti-ischemic drugs have been used in CMD patients in recent years, but all lack high-level evidence support, and their long-term efficacy in improving CMD remains uncertain. Traditional Chinese medicine, with its multi-target, multi-pathway, and multi-component characteristics, demonstrates notable effects in regulating the internal environment, improving metabolic disturbances, dilating coronary microvessels, and increasing myocardial perfusion, though further clinical validation and mechanistic investigation are needed. For overweight and obese patients with CMD and MetS who respond poorly to exercise and pharmacological therapy, gastrointestinal metabolic surgery may be considered. Such procedures effectively control blood pressure and glucose and reduce cardiovascular events beyond weight reduction. For hyperlipidemia patients with poor response to pharmacological therapy, lipoprotein apheresis may be performed. Previous studies have shown that lipoprotein apheresis effectively improves coronary microvascular function and increases myocardial perfusion.

4 Future Research Directions

The field of CMD and MetS research still faces many unresolved questions requiring further investigation to elucidate pathogenic mechanisms and improve treatment efficacy. Specific future research directions may include: (1) exploring the genetic basis of CMD and MetS through large-scale genomic studies; (2) investigating pathophysiological changes and molecular mechanisms to clarify disease progression and influencing factors; (3) developing personalized treatment strategies considering individual patient differences and needs; (4) expanding pharmacological options by identifying novel therapeutic targets and agents and evaluating their safety and efficacy; and (5) emphasizing whole-person health management by integrating physical, psychological, and social interventions and evaluating their long-term effects.

Conclusion

CMD and MetS are two closely related diseases with complex and diverse pathogenic mechanisms. Current treatment methods and medication recommendations remain controversial and inadequate, requiring more evidence-based support. Existing research demonstrates that health behavior interventions form the foundation for preventing and treating CMD and MetS, while pharmacological therapy represents an important disease management tool. Additionally, traditional Chinese medicine shows promise in treating CMD and MetS but requires further clinical validation and mechanistic investigation. In summary, CMD and MetS continue to represent major challenges in medicine, with urgent need for in-depth research to clarify pathogenic mechanisms and improve treatment approaches. Simultaneously, public health education must be strengthened to enhance health awareness and behavioral patterns for effective prevention and control of CMD and MetS.

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