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Insulin resistance and coronary microvascular dysfunction: molecular mechanisms, clinical evidence, and therapeutic perspectives

Abstract

Coronary microvascular dysfunction (CMD) represents a pathological impairment in the regulation of coronary microcirculatory blood flow, occurring in the absence of obstructive epicardial coronary artery disease. Insulin resistance (IR), a central feature of cardiometabolic disorders such as type 2 diabetes mellitus and metabolic syndrome, plays a pivotal role in vascular pathology. IR impairs insulin signaling via the IRS/PI3K/Akt pathway, reducing nitric oxide bioavailability while enhancing vasoconstrictive and pro-inflammatory signaling through the MAPK pathway. These alterations promote endothelial dysfunction, oxidative stress, inflammation, and structural remodeling of the coronary microvasculature. Clinical and experimental evidence consistently demonstrate an association between IR and CMD, even in the absence of overt diabetes, underscoring the role of IR as an early mediator of microvascular disease. Importantly, CMD is increasingly recognized as a mechanistic link between metabolic abnormalities and adverse cardiovascular outcomes, including heart failure with preserved ejection fraction (HFpEF) and microvascular angina. Therapeutic interventions aimed at improving insulin sensitivity, such as lifestyle modification, metformin, GLP-1 receptor agonists, and SGLT2 inhibitors, have shown promising effects on endothelial function and microvascular health. However, diagnostic challenges persist, and IR-related CMD remains underrepresented in clinical trials. This review summarizes current knowledge on the pathophysiological mechanisms linking IR and CMD, the clinical evidence supporting their association, and potential therapeutic strategies. Understanding these interactions may enable earlier identification and intervention in at-risk patients, ultimately reducing the burden of cardiometabolic disease.

Keywords: coronary microvascular dysfunction, insulin resistance, endothelial dysfunction, oxidative stress, heart failure with preserved ejection fraction (HFpEF)

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Introduction

Coronary microvascular dysfunction (CMD) has emerged as a clinically significant contributor to myocardial ischemia, angina, and adverse cardiovascular outcomes in the absence of obstructive epicardial coronary artery disease. CMD occurs in both diabetic and non-diabetic individuals, underscoring its role as an early manifestation of vascular dysfunction across diverse populations.[1] Epidemiological data indicate that a substantial proportion of patients presenting with angina but normal coronary angiography findings actually exhibit CMD, suggesting that the true burden of this condition remains underestimated.[2]

Insulin resistance (IR) is a central pathophysiological hallmark of cardiometabolic disorders, including type 2 diabetes mellitus (T2DM), metabolic syndrome, and obesity. It is defined by reduced tissue responsiveness to insulin, leading to compensatory hyperinsulinemia and a cascade of metabolic and vascular abnormalities.[3,4]

The association between IR and cardiovascular disease extends beyond large-vessel atherosclerosis. Growing evidence points to a key role of IR in the development of microvascular pathology, particularly within the coronary circulation.[5] Mechanistically, IR disrupts endothelial insulin signaling, shifting the balance from nitric oxide–mediated vasodilation toward vasoconstrictive and proliferative pathways.[6] In addition, IR promotes low-grade inflammation, oxidative stress, and structural remodeling of the microvasculature, all of which impair myocardial perfusion.[7]

The rationale for reviewing the interplay between IR and CMD is threefold. First, CMD represents a clinically important but often under-recognized manifestation of vascular disease. Second, IR is globally prevalent due to rising rates of obesity, sedentary behavior, and population aging. Third, elucidating the molecular mechanisms linking IR and CMD may open new opportunities for targeted prevention and therapy.

This review aims to summarize the current understanding of coronary microvascular physiology, the pathophysiology of CMD, and the molecular basis of IR. It will then explore mechanistic links between IR and CMD, review clinical evidence supporting their association, and discuss therapeutic implications and future research directions.

Physiology of coronary microcirculation

The coronary microcirculation is a finely regulated vascular network that ensures myocardial oxygen delivery aligns precisely with metabolic needs. While the epicardial coronary arteries (>500 μm) primarily serve as conductance vessels with minimal resistance, the microvasculature, comprising pre-arterioles, arterioles, capillaries, and venules, accounts for most of the coronary vascular resistance and exerts critical control over perfusion.[8]

Pre-arterioles (100–500 μm) distribute flow from the epicardial arteries to smaller arterioles and primarily respond to changes in perfusion pressure. Arterioles (20–100 μm) are the key regulators

of vascular tone and resistance, dynamically adjusting diameter in response to metabolic, endothelial, and neurohumoral signals to balance oxygen supply and demand. Capillaries (<10 μm) mediate gas and nutrient exchange, and their density determines the efficiency of oxygen diffusion; capillary rarefaction is a characteristic finding in diabetes and heart failure.[9] Venules and postcapillary vessels facilitate venous drainage and play a role in inflammation and microvascular permeability.

Coronary blood flow regulation relies on several interdependent mechanisms. Metabolic control couples myocardial oxygen consumption to perfusion through mediators such as adenosine, ATP-sensitive potassium channels, and hydrogen ions. Myogenic regulation maintains autoregulation by enabling arterioles to constrict in response to increased pressure, stabilizing flow despite fluctuations in systemic perfusion. Endothelial control is central to microvascular physiology: nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factors act as vasodilators, counterbalanced by endothelin-1 and thromboxane A2. Loss of endothelial integrity disrupts this equilibrium and contributes to the development of CMD.[10] Neurohumoral influences further refine tone, sympathetic activation through β2-adrenergic pathways promotes vasodilation, whereas α-adrenergic activation induces constriction, particularly in pathological states. Finally, extravascular compression, especially during systole, limits subendocardial perfusion and predisposes this region to ischemia in conditions like hypertrophy or elevated left-ventricular filling pressure.[11]

Coronary flow reserve (CFR), defined as the ratio of maximal hyperemic to resting coronary flow, serves as a key index of both epicardial and microvascular function. A CFR below 2.0 reflects impaired microvascular dilation and correlates strongly with adverse cardiovascular outcomes, even when epicardial arteries appear normal.[12]

Adaptation of the coronary microcirculation occurs under both physiological and pathological stimuli. Chronic hypertension induces medial hypertrophy of arterioles and capillary rarefaction, increasing resistance. In diabetes, oxidative stress and accumulation of advanced glycation end-products cause endothelial dysfunction and thickening of the basement membrane. Conversely, exercise training and athlete's heart are associated with increased capillary density and arteriolar diameter to enhance oxygen delivery.[13]

In summary, the coronary microcirculation integrates metabolic, myogenic, endothelial, neurohumoral, and mechanical influences to maintain optimal myocardial perfusion. Subtle disturbances in any of these mechanisms can impair vasodilatory reserve, precipitate ischemia, and ultimately contribute to coronary microvascular dysfunction, a crucial intermediary linking cardiometabolic disease to clinical cardiovascular events.[14]

Pathophysiology of coronary microvascular dysfunction (CMD)

Coronary microvascular dysfunction (CMD) is defined as an impairment in the regulation of coronary blood flow despite the absence of obstructive epicardial coronary artery disease. The disorder arises from the combined effects of structural remodeling, endothelial dysfunction, vascular smooth muscle abnormalities, inflammation, and neurohumoral or extravascular influences. These mechanisms converge to reduce vasodilatory capacity, increase vasoconstrictive reactivity, and ultimately compromise myocardial perfusion.[14]

Structural alterations

Anatomical remodeling of the coronary microvasculature is a central component of CMD. Chronic hypertension promotes arteriolar medial hypertrophy and wall thickening, which narrow the lumen and elevate vascular resistance. In parallel, capillary rarefaction decreases perfusion density and impairs oxygen diffusion, particularly in hypertensive heart disease and diabetic cardiomyopathy.[13] Thickening of the basement membrane, a hallmark of diabetes mellitus, further restricts oxygen exchange and increases vascular stiffness. In many cases, perivascular fibrosis resulting from extracellular matrix accumulation limits vessel compliance and blunts vasodilatory responsiveness.[15]

Endothelial dysfunction

Endothelial dysfunction represents the functional core of CMD. Under physiological conditions, the endothelium maintains a dynamic equilibrium between vasodilators and vasoconstrictors. In CMD, oxidative stress disrupts this balance by reducing nitric oxide (NO) bioavailability through uncoupling of endothelial NO synthase (eNOS). Concomitantly, the expression of endothelin-1 is elevated, enhancing vasoconstriction and stimulating vascular remodeling. The net effect is a blunted response to endothelium-dependent stimuli such as acetylcholine and shear stress, reflecting the loss of endothelial sensitivity.[16]

Vascular smooth muscle dysfunction

Beyond the endothelium, intrinsic alterations in vascular smooth muscle cells (VSMCs) contribute to abnormal vasomotion. Reduced responsiveness to adenosine, prostacyclin, and exogenous NO donors has been demonstrated in CMD, signifying impaired vasodilatory signaling. At the same time, VSMCs show heightened reactivity to vasoconstrictors such as catecholamines, angiotensin II, and endothelin-1. Dysregulated intracellular calcium handling enhances vascular tone and limits relaxation, reinforcing microvascular constriction.[5]

Inflammation and oxidative stress

Chronic low-grade inflammation and oxidative stress play pivotal roles in CMD pathogenesis. Circulating cytokines such as tumor necrosis factor-α and interleukin-6 impair endothelial NO synthesis and promote vascular remodeling. Reactive oxygen species (ROS), generated through mitochondrial dysfunction and NADPH oxidase activation, scavenge NO and trigger direct oxidative injury to vascular components.[17] Histopathologic analyses have revealed perivascular macrophage and T-cell infiltration, supporting an immunologic dimension to microvascular injury.

Neurohumoral and extravascular factors

Neurohumoral dysregulation further aggravates CMD. Sympathetic overactivity heightens microvascular tone via α-adrenergic stimulation, particularly in stress-induced ischemia. Activation of the renin–angiotensin–aldosterone system (RAAS) drives oxidative stress, inflammation, and arteriolar hypertrophy through angiotensin II–mediated signaling. Extravascular compression, especially from elevated left-ventricular end-diastolic pressure or myocardial hypertrophy, impedes subendocardial flow and accentuates ischemic vulnerability.[18]

Heterogeneity of CMD phenotypes

CMD is not a uniform entity but rather a spectrum encompassing multiple overlapping phenotypes. Some patients exhibit endothelium-

dependent dysfunction, marked by impaired vasodilation in response to acetylcholine, while others show endothelial-independent impairment with blunted response to adenosine or nitrovasodilators. In certain cases, microvascular spasm or fixed structural remodeling predominates. This heterogeneity explains the diverse clinical presentations of CMD, from exertional angina to silent ischemia and heart failure with preserved ejection fraction (HFpEF).[1]

Consequences for myocardial function

Functionally, CMD leads to ischemia due to inadequate augmentation of flow during stress. Chronic hypoperfusion fosters interstitial fibrosis, which contributes to diastolic dysfunction and the development of HFpEF. Over time, microvascular insufficiency alters myocardial structure and electrophysiology, increasing the risk of arrhythmias and adverse remodeling.[19]

In summary, the pathophysiology of CMD reflects a convergence of structural, endothelial, inflammatory, and neurohumoral processes acting within the coronary microvasculature. These disturbances link systemic cardiometabolic disorders such as hypertension, diabetes, and obesity to microvascular ischemia and heart failure. Understanding the cellular and molecular basis of CMD provides a critical framework for developing diagnostic and therapeutic strategies aimed at restoring coronary microvascular integrity.

Insulin resistance: definition, mechanisms, and systemic effects

Definition and epidemiology

Insulin resistance (IR) is a pathological state in which insulin-sensitive tissues, including skeletal muscle, adipose tissue, and liver, fail to respond adequately to normal circulating concentrations of insulin. This diminished responsiveness leads to compensatory hyperinsulinemia to preserve glucose homeostasis. IR constitutes a core abnormality in type 2 diabetes mellitus (T2DM) and metabolic syndrome but also occurs in obesity, hypertension, dyslipidemia, and polycystic ovary syndrome.[3] Epidemiologically, IR affects over one billion individuals worldwide, paralleling the global escalation of obesity and physical inactivity.[4]

Cellular and molecular mechanisms of insulin resistance

Under physiological conditions, insulin binding to its receptor, a transmembrane tyrosine kinase, activates insulin receptor substrate (IRS-1/2) proteins, which engage the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This signaling cascade facilitates glucose transporter type 4 (GLUT4) translocation to the cell surface, enabling glucose uptake. In endothelial cells, the same PI3K/Akt axis activates endothelial nitric oxide synthase (eNOS), promoting nitric oxide (NO) release and vasodilation.[6]

In insulin resistance, several defects impair this cascade. Serine phosphorylation of IRS proteins, triggered by free fatty acids, inflammatory cytokines, and oxidative stress, hampers downstream PI3K/Akt activation. Meanwhile, the mitogen-activated protein kinase (MAPK) pathway remains relatively preserved, driving vasoconstrictive, mitogenic, and pro-inflammatory signaling.[20] Mitochondrial dysfunction impedes fatty acid oxidation and augments reactive oxygen species (ROS) generation, compounding cellular stress. In addition, ectopic lipid accumulation within skeletal muscle and hepatocytes, termed lipotoxicity, disrupts receptor function and aggravates metabolic impairment.[21]

Systemic effects of insulin resistance

Metabolic effects: Hepatic insulin resistance enhances gluconeogenesis, producing fasting hyperglycemia, while impaired glucose uptake in skeletal muscle leads to postprandial hyperglycemia. Adipose tissue insulin resistance increases lipolysis and circulating free fatty acids, reinforcing systemic IR through feedback mechanisms.[22]

Vascular effects: In endothelial cells, defective PI3K/Akt signaling reduces NO bioavailability, whereas intact MAPK activity amplifies endothelin-1 (ET-1) synthesis, favoring vasoconstriction and vascular stiffness.[23] Chronic hyperinsulinemia also augments sympathetic outflow, raising peripheral resistance and arterial pressure.[24]

Inflammatory and oxidative stress effects: Dysfunctional adipose tissue in insulin-resistant states secretes pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), while production of adiponectin, an anti-inflammatory and vasoprotective adipokine, is reduced. The resulting low-grade inflammation promotes endothelial dysfunction and vascular remodeling through oxidative injury.[25]

Cardiac effects: IR contributes directly to myocardial lipotoxicity. Excess fatty acid uptake exceeds oxidative capacity, leading to lipid accumulation, mitochondrial stress, and contractile dysfunction. Sustained hyperinsulinemia alters calcium cycling and myocardial energetics, promoting diastolic dysfunction and impaired relaxation.[26]

Neurohumoral activation: Hyperinsulinemia enhances renal sodium reabsorption and activates the renin–angiotensin–aldosterone system (RAAS), thereby increasing blood volume and systemic pressure (Table 1).[27]

Table 1 Systemic and cardiovascular effects of ınsulin resistance

Domain	Primary mechanism	Physiological consequence	References
Metabolic	Impaired GLUT4 translocation; ↑ hepatic gluconeogenesis	Fasting and postprandial hyperglycemia	3, 4, 22
Endothelial / Vascular	↓ PI3K/Akt/eNOS pathway, ↑ MAPK/ET-1 signaling	↓ NO bioavailability, ↑ vasoconstriction, endothelial dysfunction	6, 20, 23
Inflammatory / Oxidative	↑ TNF-α, IL-6, ↓ adiponectin; mitochondrial ROS generation	Chronic inflammation, vascular remodeling, oxidative injury	25, 31, 34
Cardiac	↑ Fatty acid uptake, mitochondrial overload, lipotoxicity	Diastolic dysfunction, myocardial steatosis	26, 35
Neurohumoral	↑ Sympathetic activation, ↑ RAAS activity	Hypertension, sodium retention, vascular hypertrophy	24, 27

Abbreviations: PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase; MAPK, mitogen-activated protein kinase; ET-1, endothelin-1; NO, nitric oxide; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; GLUT4, glucose transporter type 4.

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Clinical consequences of insulin resistance

IR is an independent determinant of cardiovascular morbidity and mortality, even without overt diabetes. It accelerates atherosclerosis through endothelial dysfunction, inflammation, and plaque instability.[28] In heart failure with preserved ejection fraction (HFpEF), IR drives microvascular inflammation, interstitial fibrosis, and impaired diastolic compliance.[29] Importantly, IR contributes to coronary microvascular dysfunction (CMD) by disrupting endothelial vasodilatory signaling and promoting vascular remodeling, linking metabolic abnormalities to myocardial ischemia in both diabetic and non-diabetic individuals.[30]

In summary, insulin resistance represents a multifaceted pathophysiological state encompassing molecular defects in insulin signaling, mitochondrial dysfunction, oxidative stress, and inflammation. The selective impairment of PI3K/Akt signaling with relative preservation of MAPK signaling constitutes a critical molecular switch that converts insulin's normally vasodilatory effects into pro-constrictive and pro-inflammatory actions. Through these mechanisms, IR serves as a fundamental driver connecting metabolic dysregulation to coronary microvascular dysfunction and cardiovascular disease.

Mechanistic links between IR and CMD

Insulin resistance (IR) and coronary microvascular dysfunction (CMD) represent interdependent pathophysiological processes that reinforce one another. Although CMD can arise independently of traditional cardiovascular risk factors, IR serves as a central upstream determinant of microvascular impairment. The molecular disturbances of IR, affecting endothelial signaling, oxidative balance, inflammation, and structural integrity, culminate in the vascular abnormalities that define CMD (Table 2).[20]

Table 2 Mechanistic pathways linking ınsulin resistance and coronary microvascular dysfunction

Mechanistic domain	Molecular pathway	Key effect on microcirculation	Ref. No
Endothelial dysfunction	↓ PI3K/Akt/eNOS signaling, ↑ MAPK/ET-1 axis	Reduced NO bioavailability, increased vasoconstriction	6, 20, 23
Oxidative stress	↑ NADPH oxidase activity, mitochondrial ROS, AGE formation	NO scavenging, endothelial injury, vascular stiffness	17, 31, 32
Inflammation	↑ TNF-α, IL-6, MCP-1; ↓ adiponectin	Endothelial activation, immune cell infiltration, remodeling	25, 33, 34
Structural remodeling	TGF-β activation, capillary rarefaction, perivascular fibrosis	Reduced perfusion reserve, vascular stiffening	13, 15, 29
Neurohumoral activation	↑ RAAS, ↑ sympathetic tone	Microvascular constriction, hypertrophy	18, 24, 37

Abbreviations: PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase; MAPK, mitogen-activated protein kinase; ET-1, endothelin-1; NO, nitric oxide; ROS, reactive oxygen species; AGE, advanced glycation end-product; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; TGF-β, transforming growth factor-beta; RAAS, renin–angiotensin–aldosterone system; CMD, coronary microvascular dysfunction.

Endothelial insulin signaling imbalance

A primary mechanistic link between IR and CMD is the selective disruption of insulin signaling within endothelial cells. Under normal conditions, insulin stimulates the PI3K/Akt pathway, leading to activation of endothelial nitric oxide synthase (eNOS) and increased nitric oxide (NO) production, critical for vasodilation and anti-inflammatory regulation. In insulin-resistant states, this pathway is blunted, causing diminished NO bioavailability.[6] Conversely, the mitogen-activated protein kinase (MAPK) pathway, which promotes vasoconstriction, endothelin-1 release, and smooth muscle proliferation, remains relatively preserved or even overactive.[23] The result is a functional imbalance in endothelial signaling that favors vasoconstriction and inflammation, establishing the vascular milieu characteristic of CMD.[1]

Oxidative stress and nitric oxide scavenging

IR provokes excessive oxidative stress through multiple convergent pathways. Elevated free fatty acids enhance mitochondrial reactive oxygen species (ROS) generation, while hyperglycemia and advanced glycation end products (AGEs) further amplify ROS production. In addition, NADPH oxidase activation reinforces oxidative injury.[31] ROS directly reacts with NO to form peroxynitrite, reducing NO bioavailability and damaging proteins and lipids within the endothelium. This oxidative stress–inflammation loop perpetuates microvascular dysfunction and impairs vasodilatory reserve.[32]

Low-grade inflammation and immune activation

Adipose tissue in insulin-resistant states secretes pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1 while downregulating adiponectin, a protective adipokine with vasodilatory and anti-inflammatory properties.[25] These mediators impair insulin signaling in the endothelium and recruit immune cells into perivascular spaces. Macrophage infiltration and T-cell activation have been observed in experimental models of IR and are associated with microvascular rarefaction, fibrosis, and loss of vascular reactivity.[33] Chronic immune activation thereby links metabolic dysfunction to structural and functional microvascular injury.[34]

Structural microvascular remodeling

Sustained IR promotes morphological changes in the coronary microvasculature that restrict perfusion capacity. Capillary rarefaction diminishes microvascular density and oxygen diffusion, while basement membrane thickening and perivascular fibrosis, driven by hyperglycemia, hyperinsulinemia, and transforming growth factor-β (TGF-β) signaling, impair compliance and hinder vasodilation.[13] These fixed structural changes exacerbate the functional endothelial abnormalities that typify CMD.

Altered myocardial substrate metabolism

IR shifts myocardial substrate utilization toward predominant fatty acid oxidation, which is less oxygen-efficient compared with glucose metabolism. This metabolic inflexibility increases myocardial oxygen

consumption per unit of ATP generated, predisposing to subendocardial ischemia under stress conditions.[35] Lipid intermediates such as ceramides and diacylglycerols accumulate within cardiomyocytes, causing mitochondrial dysfunction, apoptosis, and impaired communication between endothelial and myocardial cells, further compounding CMD.[26]

Microvascular dysfunction as a precursor to HFpEF

The IR–CMD axis is now recognized as a major contributor to heart failure with preserved ejection fraction (HFpEF). IR promotes systemic inflammation, oxidative stress, and capillary rarefaction, while CMD reduces coronary flow reserve and subendocardial perfusion. The combined effect is chronic ischemia leading to myocardial fibrosis, impaired relaxation, and diastolic dysfunction.[29] CMD thus represents the microvascular manifestation of IR that precedes and sustains HFpEF progression.

Gender-specific differences

CMD exhibits sex-related differences, with women, particularly postmenopausal women, showing greater susceptibility in the presence of IR (36). Estrogen normally enhances endothelial NO production; therefore, its loss accentuates IR-induced endothelial dysfunction. This helps explain the higher prevalence of microvascular angina and CMD in women despite angiographically normal coronary arteries.

Neurohumoral activation

Hyperinsulinemia in IR states activates the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS). Both pathways elevate vascular tone and foster remodeling. Angiotensin II, in particular, drives oxidative stress and inflammation, further impairing endothelial function and reinforcing the IR–CMD cycle.[37]

In summary, insulin resistance fosters coronary microvascular dysfunction through a multilevel network of metabolic and vascular disturbances. At the endothelial level, selective impairment of PI3K/Akt signaling with preserved MAPK activation converts insulin's vasodilatory effect into a vasoconstrictive one. At the systemic level, inflammation, oxidative stress, and neurohumoral activation amplify microvascular damage. At the myocardial level, altered substrate metabolism increases oxygen demand while reducing perfusion efficiency. These interwoven mechanisms explain the strong epidemiologic and mechanistic connection between IR and CMD, providing the rationale for targeting metabolic pathways to restore microvascular health.

Clinical evidence linking IR and CMD

The relationship between insulin resistance (IR) and coronary microvascular dysfunction (CMD) has been corroborated by experimental, observational, and interventional data. Across diverse populations, IR consistently predicts microvascular impairment independent of diabetes status or obstructive coronary artery disease. This evidence establishes IR not merely as a metabolic abnormality but as a key pathophysiological driver of coronary microvascular disease (Table 3).[20]

Table 3 Clinical evidence supporting the association between ınsulin resistance and coronary microvascular dysfunction

Study / cohort	Population	Diagnostic modality	Key findings	Ref. No
WISE Study	Women with angina, normal coronaries	Invasive CFR and acetylcholine testing	IR linked to reduced CFR and higher angina prevalence	39, 47
Japanese PET Cohort	Non-diabetic adults	PET perfusion imaging	IR predicted low CFR independent of BMI	40
PROMIS-HFpEF	HFpEF patients	Invasive and imaging CFR assessment	IR associated with CMD and adverse outcomes	19
Bøtker et al.	Syndrome X patients	PET and metabolic assessment	IR linked to reduced myocardial energy efficiency	38

Abbreviations: IR, insulin resistance; CMD, coronary microvascular dysfunction; PET, positron emission tomography; CFR, coronary flow reserve; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction.

Epidemiological and observational studies

Large population-based studies have shown a strong association between surrogate markers of IR and reduced coronary vasodilatory capacity. In patients with cardiac syndrome X, reduced coronary flow reserve (CFR) was independently linked to insulin resistance and altered myocardial energy metabolism, supporting the concept that metabolic dysfunction contributes directly to microvascular impairment.[38] Similarly, the Women's Ischemia Syndrome Evaluation (WISE) study found that women with IR or metabolic syndrome exhibited higher angina prevalence and reduced CFR, despite having angiographically normal coronary arteries.[39] A Japanese cohort using positron emission tomography (PET) imaging confirmed that IR predicted reduced CFR even in non-diabetic individuals, supporting the concept that CMD may precede overt diabetes.[40] Together, these findings implicate IR as an independent determinant of coronary microvascular dysfunction beyond traditional atherosclerotic mechanisms.

Imaging-based evidence

Advances in cardiac imaging have provided detailed characterization of IR-related microvascular abnormalities. PET studies consistently demonstrate that individuals with IR exhibit reduced myocardial blood flow and CFR, irrespective of epicardial coronary anatomy.[5] Stress-perfusion cardiac magnetic resonance imaging (CMR) in obese and prediabetic subjects further confirms an inverse correlation between Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels and myocardial perfusion reserve.[41] Transthoracic Doppler echocardiography, used to assess CFR in the left anterior descending artery, has yielded similar findings, with IR predicting impaired microvascular vasodilation.[42] Collectively, these modalities establish a consistent pattern of functional coronary impairment linked to insulin resistance.

Invasive hemodynamic studies

Invasive assessments during coronary angiography have directly validated these associations. Studies measuring CFR and the index of microvascular resistance (IMR) in non-diabetic individuals revealed that higher HOMA-IR scores correspond to diminished microvascular function, independent of other metabolic parameters.[43] Endothelium-dependent vasodilation assessed by acetylcholine provocation testing is also attenuated in IR, reflecting a functional endothelial defect consistent with impaired nitric oxide bioavailability.[44] These

hemodynamic data provide physiological confirmation of the molecular mechanisms connecting IR to CMD.

Experimental and translational studies

Animal models have strengthened the causal link between IR and CMD. Rodents with diet-induced insulin resistance exhibit reduced eNOS activity, heightened oxidative stress, and capillary rarefaction in the coronary circulation.[45] Furthermore, mice with targeted disruption of endothelial insulin signaling display marked impairment in vasodilation and greater susceptibility to ischemic injury.[46] These findings demonstrate that IR itself, independent of hyperglycemia, can initiate and sustain microvascular dysfunction.

Clinical consequences

The coexistence of IR and CMD carries significant prognostic implications. In the *PROMIS-HFpEF* study, patients with higher HOMA-IR scores exhibited reduced CFR, which was independently predictive of adverse outcomes.[19] Similarly, microvascular angina occurs disproportionately in individuals with IR, particularly women, highlighting the intersection between metabolic and vascular pathophysiology.[47] Longitudinal studies indicate that IR-associated CMD predicts major adverse cardiovascular events (MACE), including myocardial infarction, heart failure hospitalization, and cardiovascular death.[30]

Interventional evidence

Therapeutic interventions targeting metabolic dysfunction have demonstrated potential to improve microvascular function. Lifestyle modification, comprising exercise and caloric restriction, enhances insulin sensitivity and has been shown to improve CFR in obese and prediabetic individuals.[48] Pharmacologic approaches such as metformin therapy exert vascular benefits beyond glycemic control, restoring endothelial function and modestly increasing CFR in small-scale trials.[49] More recently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated favorable effects on endothelial function and cardiovascular outcomes, though CMD-specific data remain limited.[50]

In summary, extensive clinical and experimental data support a bidirectional relationship between IR and CMD. Insulin resistance impairs endothelial function, augments oxidative stress, and promotes vascular remodeling, thereby precipitating CMD. In turn, CMD contributes to ischemia, angina, HFpEF, and adverse cardiovascular outcomes. Notably, this link is evident even in non-diabetic and female populations, positioning CMD as an early, measurable manifestation of cardiovascular risk in insulin-resistant individuals.

Therapeutic implications

The strong mechanistic and clinical relationship between insulin resistance (IR) and coronary microvascular dysfunction (CMD) highlights the need for an integrated therapeutic approach. Because IR represents a systemic metabolic defect and CMD reflects its vascular manifestation, treatment must simultaneously address both metabolic dysregulation and endothelial dysfunction. Although no drug is specifically approved for CMD, multiple interventions, ranging from behavioral modification to pharmacologic and device-based therapies, have demonstrated benefit in improving microvascular and metabolic health (Table 4).[20]

Table 4 Therapeutic Strategies Targeting Insulin Resistance–Related Coronary Microvascular Dysfunction

Intervention	Mechanism of action	Impact on coronary microvascular function	Ref. No
Lifestyle modification (exercise, diet)	↑ Insulin sensitivity, ↓ inflammation, ↑ NO	Improves CFR and FMD in IR/metabolic syndrome	48, 51, 52
Metformin	AMPK activation, ↑ NO synthesis, ↓ oxidative stress	Improves CFR and endothelial function	49
GLP-1 receptor agonists	↓ Inflammation, ↑ NO signaling, ↓ visceral adiposity	Enhances endothelial function, possible CFR improvement	50
SGLT2 inhibitors	↓ Oxidative stress, osmotic diuresis, improved cardiac energetics	Reduces HF risk; indirect CMD improvement	54
ACEI/ARB, statins	↓ RAAS, ↓ inflammation, ↑ NO	Improves CFR, endothelial repair	59, 60
Ranolazine	Inhibits late Na+ current, improves diastolic relaxation	Improves symptoms and perfusion in CMD	58

Abbreviations: AMPK, AMP-activated protein kinase; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAAS, renin–angiotensin–aldosterone system; CFR, coronary flow reserve; FMD, flow-mediated dilation; NO, nitric oxide; Na^+, sodium ion; HF, heart failure.

Lifestyle interventions

Lifestyle modification remains the foundation of therapy for both IR and CMD. Regular aerobic exercise enhances insulin sensitivity, stimulates endothelial nitric oxide (NO) production, and improves coronary flow reserve (CFR). Controlled studies show that structured exercise programs in obese or insulin-resistant individuals restore microvascular vasodilatory capacity and reduce ischemic burden.[51] Dietary interventions, including caloric restriction and adherence to a Mediterranean-style diet, lower systemic inflammation and improve adipokine balance, thereby ameliorating endothelial dysfunction.[52] Weight reduction, particularly through bariatric surgery in morbidly obese patients, markedly improves insulin sensitivity and has been associated with recovery of myocardial perfusion reserve on non-invasive imaging.[53] These lifestyle measures form the essential first-line strategy for all insulin-resistant patients, given their dual metabolic and vascular benefits.

Glucose-lowering therapies

Several glucose-lowering agents exert vascular protective effects beyond glycemic control. Metformin, via activation of AMP-activated protein kinase (AMPK), suppresses hepatic gluconeogenesis, improves endothelial NO bioavailability, and has been shown in small trials to enhance CFR and relieve anginal symptoms in CMD.[49] GLP-1 receptor agonists improve endothelial function through anti-inflammatory effects, reduction in visceral adiposity, and increased NO signaling; recent evidence suggests these agents may also augment myocardial perfusion.[50] SGLT2 inhibitors reduce oxidative stress and myocardial workload through osmotic diuresis and improved cardiac energetics, translating into reduced heart failure events in large trials such as

EMPEROR-Reduced and *DAPA-HF*.[54] Although thiazolidinediones (TZDs) enhance insulin sensitivity by activating PPAR-γ, their fluid retention limits use in patients predisposed to heart failure, despite data suggesting improvements in endothelial function.[55]

Anti-ıschemic and anti-anginal therapies

Conventional anti-anginal drugs remain useful for symptomatic CMD. Beta-blockers lower heart rate, prolong diastolic perfusion time, and reduce myocardial oxygen consumption, indirectly improving subendocardial flow.[56] Calcium channel blockers alleviate microvascular spasm and enhance vasodilation, though their effects on insulin sensitivity are limited.[57] Ranolazine, by inhibiting late sodium current, improves diastolic relaxation and reduces ischemia; small randomized trials have demonstrated symptom improvement in microvascular angina.[58] In contrast, nitrates are often ineffective in CMD because their vasodilatory action preferentially targets large coronary arteries.[14]

Agents targeting endothelial dysfunction

ACE inhibitors and angiotensin receptor blockers (ARBs) reduce angiotensin II–mediated oxidative stress and inflammation, enhancing NO availability and improving CFR.[59] Statins, through lipid-independent pleiotropic effects, stabilize the endothelium, suppress inflammation, and enhance microvascular responsiveness.[60] Antioxidant therapies, though conceptually appealing, have produced inconsistent clinical outcomes; targeted inhibition of NADPH oxidase and mitochondrial oxidative pathways remains under investigation.[31]

Novel and emerging therapies

Emerging approaches aim to directly target endothelial or inflammatory mechanisms. L-arginine supplementation provides substrate for NO synthesis and may transiently improve endothelial function, though results are heterogeneous.[61] Phosphodiesterase-5 inhibitors (e.g., sildenafil) enhance cyclic GMP signaling and have demonstrated microvascular and symptomatic benefits in small CMD cohorts.[62] Anti-inflammatory strategies, including IL-1β blockade with canakinumab, have shown cardiovascular event reduction in large trials and may hold promise for CMD associated with IR.[63] Experimental cell-based regenerative therapies, using endothelial progenitor cells or mesenchymal stem cells, are under early-phase investigation for restoration of microvascular density and perfusion.[64]

Sirtuin 1 (SIRT1) represents a promising molecular target in the management of insulin resistance–associated CMD. SIRT1 enhances endothelial nitric oxide synthase (eNOS) activity, increases nitric oxide bioavailability, and promotes vasodilation, while also regulating insulin secretion from pancreatic β-cells. Experimental studies indicate that SIRT1 activation suppresses oxidative stress and inflammation, thereby improving endothelial and microvascular function. Accordingly, SIRT1 activators such as resveratrol or NAD^+-boosting agents may exert both metabolic and vascular benefits. Conversely, reduced SIRT1 activity or pharmacologic inhibition could aggravate cardiometabolic dysfunction. Future therapeutic strategies might integrate SIRT1 activation with established insulin-sensitizing agents (e.g., metformin, GLP-1 receptor agonists, or SGLT2 inhibitors) to achieve synergistic improvement in vascular and metabolic health.[65,66]

Device-based therapies

For patients with refractory CMD-related angina, device-based interventions offer alternative strategies. The coronary sinus reducer, by elevating venous pressure and redistributing flow toward ischemic subendocardial regions, has improved symptoms and quality of life in small clinical studies.[67] Enhanced external counterpulsation augments diastolic coronary perfusion and promotes collateral vessel development, providing symptomatic relief and improved functional capacity in CMD.[68]

In summary, therapeutic management of CMD in the context of insulin resistance requires a multifaceted, individualized approach. Lifestyle modification remains the cornerstone of therapy, while pharmacologic agents such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors show promise in targeting both metabolic and vascular abnormalities. Traditional anti-anginal therapies address symptoms but not the underlying metabolic derangement. Future directions include therapies aimed at endothelial restoration, oxidative balance, and inflammation control. Integrating metabolic correction with vascular protection represents the optimal strategy for preventing and reversing CMD in insulin-resistant individuals.

Future directions and research gaps

Despite major progress in elucidating the relationship between insulin resistance (IR) and coronary microvascular dysfunction (CMD), significant scientific and clinical uncertainties persist. CMD is increasingly recognized as a distinct and prognostically important cardiovascular phenotype, yet remains underdiagnosed and undertreated. Addressing current gaps in diagnostics, biomarkers, longitudinal data, and therapeutics is critical to advance prevention and management strategies (Table 5).[14]

Table 5 Future directions and research gaps in IR-associated coronary microvascular dysfunction

Domain	Current limitation	Research priority	Potential approach	Ref. No
Diagnostics	Invasive, costly, non-standardized	Develop accessible non-invasive CMD detection	PET/CMR + circulating biomarkers	1, 14
Biomarkers	No validated biomarker for CMD	Identify multi-omic molecular signatures	Genomic, proteomic, metabolomic integration	67
Therapeutic trials	Lack of CMD-specific endpoints	Test metabolic–vascular therapies on CMD outcomes	GLP-1RA, SGLT2i, anti-inflammatory trials	49, 50, 63
Sex differences	CMD underdiagnosed in women	Investigate hormonal and endothelial differences	Estrogen–IR–NO pathway studies	36
Basic science	Incomplete understanding of endothelial insulin signaling	Explore PI3K/Akt vs MAPK dominance, oxidative stress	Translational endothelial models	6, 20, 64

Abbreviations: CMD, coronary microvascular dysfunction; IR, insulin resistance; PET, positron emission tomography; CMR, cardiac magnetic resonance imaging; HFpEF, heart failure with preserved ejection fraction; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; AI, artificial intelligence; TGF-β, transforming growth factor-beta.

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Refinement of diagnostic tools

Current diagnostic modalities for CMD, such as coronary flow reserve (CFR) and the index of microvascular resistance (IMR), are invasive and limited to specialized centers. Non-invasive techniques like positron emission tomography (PET) and cardiac magnetic resonance (CMR) imaging offer high accuracy but are costly and not widely accessible. Development of standardized, low-cost diagnostic algorithms integrating imaging data with circulating biomarkers could allow earlier and broader detection of CMD in insulin-resistant populations.[1]

Biomarker development

No validated biomarkers reliably diagnose CMD or monitor disease progression. Candidates such as asymmetric dimethylarginine (ADMA), high-sensitivity CRP, and oxidative stress markers show potential but lack specificity. Multi-omics platforms, integrating genomic, transcriptomic, proteomic, and metabolomic data, may yield unique biomarker signatures that identify early endothelial dysfunction linked to IR.[69]

Longitudinal and large-scale studies

Most evidence linking IR and CMD arises from cross-sectional or small-scale cohorts. Large, prospective population studies are required to establish causality and to define whether CMD precedes overt diabetes or predicts cardiovascular events independently of traditional risk factors. Standardized CMD endpoints (e.g., CFR, IMR) should be incorporated into future epidemiologic and outcomes trials.[19]

Therapeutic trials targeting IR-associated CMD

While glucose-lowering agents such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors have proven cardiovascular benefit, few trials have specifically evaluated their impact on CMD endpoints. Randomized studies directly measuring improvements in microvascular function and clinical symptoms are needed to guide therapeutic decision-making. Similarly, anti-inflammatory therapies (e.g., IL-1β blockade) and agents targeting oxidative stress merit investigation in dedicated CMD populations.[63]

Personalized medicine approaches

CMD encompasses diverse pathophysiologic mechanisms with varying degrees of contribution from IR. Integration of clinical, imaging, and molecular data could enable individualized diagnosis and risk stratification. Artificial intelligence and machine learning techniques may enhance prediction of CMD phenotypes and optimize therapy selection across heterogeneous patient populations.[70]

Sex and gender considerations

Women with IR are disproportionately affected by CMD, particularly in postmenopausal stages. Sex-specific research examining the influence of estrogen, microvascular gene expression, and psychosocial factors could illuminate unique disease mechanisms and improve therapeutic precision for female patients.[36]

Translational and basic science

Mechanistic studies remain essential to clarify how IR alters microvascular signaling networks, including PI3K/Akt, MAPK, and mitochondrial pathways, and to identify therapeutic targets capable of restoring endothelial homeostasis. Preclinical models should also evaluate regenerative strategies aimed at reversing microvascular rarefaction and fibrosis through endothelial progenitor or stem cell–based approaches.[64]

Future investigations should clarify the mechanistic role of SIRT1 signaling in linking insulin resistance with coronary microvascular dysfunction. SIRT1 modulates nitric oxide synthesis, mitochondrial function, and redox homeostasis, yet its precise contribution to microvascular regulation remains incompletely defined. Measurement of plasma SIRT1 concentrations may serve as a potential biomarker for disease progression and treatment response in cardiometabolic disorders. Translational studies are warranted to explore how SIRT1 activators influence vascular repair, epigenetic remodeling, and endothelial rejuvenation. Large-scale clinical trials should determine whether pharmacologic enhancement of SIRT1 can improve coronary flow reserve and clinical outcomes in insulin-resistant populations.[71,72]

In summary, future progress will depend on bridging gaps between bench and bedside. Standardized diagnostic criteria, validated biomarkers, and targeted interventions must be established to formally position CMD as a treatable complication of IR. Multidisciplinary collaboration among cardiologists, endocrinologists, and vascular biologists is vital to integrate metabolic and vascular research into clinical application.

Conclusion

Coronary microvascular dysfunction (CMD) represents a prevalent yet underrecognized manifestation of cardiovascular disease in insulin-resistant states. Mechanistically, IR drives CMD through endothelial signaling imbalance, oxidative stress, inflammation, and structural remodeling of the coronary microcirculation. Clinical studies consistently demonstrate that CMD occurs frequently in insulin-resistant individuals, even without overt diabetes or obstructive coronary disease, and predicts angina, ischemia, heart failure with preserved ejection fraction (HFpEF), and adverse cardiovascular outcomes.

Therapeutic management centers on lifestyle modification and risk factor control. Pharmacologic therapies that improve insulin sensitivity, such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors, hold particular promise for reversing CMD-related vascular dysfunction. Traditional anti-anginal agents provide symptomatic relief but do not address the metabolic roots of the disease. Dedicated clinical trials are urgently needed to define evidence-based treatment strategies specifically targeting IR-associated CMD.

In conclusion, CMD should be viewed as the vascular expression of insulin resistance, a pathophysiological bridge between metabolic dysfunction and clinical cardiovascular disease. A comprehensive, multi-layered approach combining early detection, metabolic correction, endothelial protection, and targeted therapy may significantly reduce the burden of cardiometabolic disease worldwide.

Contributorship

All of the authors contributed planning, conduct, and reporting of the work. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests

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