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# Obesity and Coronary Microvascular Disease – Implications for Adipose Tissue-Mediated Remote Inflammatory Response

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## Abstract

It is believed that obesity has detrimental effects on the coronary circulation. These include immediate changes in coronary arterial vasomotor responsiveness and the development of occlusive large coronary artery disease. Despite its critical role in regulating myocardial perfusion, the altered behavior of coronary resistance arteries, which gives rise to coronary microvascular disease (CMD) is poorly understood in obesity. A chronic, low-grade vascular inflammation has been long considered as one of the main underlying pathology behind CMD. The expanded adipose tissue and the infiltrating macrophages are the major sources of pro-inflammatory mediators that have been implicated in causing inadequate myocardial perfusion and, in a long term, development of heart failure in obese patients. Much less is known the mechanisms regulating the release of these cytokines into the circulation that enable them to exert their remote effects in the coronary microcirculation. This mini review aims to examine recent studies describing alterations in the vasomotor function of coronary resistance arteries and the role of adipose tissue-derived pro-inflammatory cytokines and adipokines in contributing to CMD in obesity. We provide examples of regulatory mechanisms by which adipokines are released from adipose tissue to exert their remote inflammatory effects on coronary microvessels. We identify some of the important challenges and opportunities going forward.

### Keywords

Obesity; coronary artery; adipose tissue; TNF; leptin; resistin; IL-6; adiponectin

## INTRODUCTION

Obese patients have a higher prevalence of cardiovascular complications contributing to the morbidity and mortality, which in turn accounts for substantial direct and indirect medical and social costs in the United States. Diagnosis and treatment of obstructive large coronary artery disease are established and, for the most part, effective. However, even in the absence of significant occlusion of large coronary arteries, obese patients frequently exhibit evidence

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**CONFLICT OF INTEREST**
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of myocardial ischemia. Recent studies have identified that myocardial ischemia is often due to abnormalities in the coronary microcirculation. Despite its critical role in regulating myocardial perfusion, the altered behavior of resistance arteries, which gives rise to coronary microvascular disease (CMD) is poorly understood. CMD is characterized by small artery vasospasm and microvascular obstruction, and is generally found in patients with type-2 diabetes. Morphological changes in microvessels are quite rare in obesity prior to the development of hyperglycemia and type 2 diabetes. It has been the view that blood flow to various organs is rarely impaired in obesity, unless occlusive atherosclerosis of the larger arteries develops. Throughout life organs receive normal or even greater than normal blood flow in uncomplicated obesity [1]. This paradigm has been challenged in recent years. Studies reported reduced myocardial perfusion in obese patients [2–5], while others have found that myocardial perfusion is not compromised in obesity [6]. Reduced myocardial perfusion can be due to the reduced vasodilator capacity of coronary resistance vessels, which in some instances represents important markers of cardiovascular risk or may contribute to the pathogenesis of obesity. The underlying mechanisms responsible for reduced vasodilator function of coronary microvessels in obesity, however, remained elusive.

The pathological role and treatment of atherogenic dyslipidemia in the development of obesity-associated large coronary artery disease are well established [7]. In obesity, the endocrine function of adipocytes is altered, which is manifested as reduced adiponectin [8] and elevated levels of leptin, resistin, IL-6 and tumor necrosis factor (TNF) [9]. It has been shown that in obesity, adipocyte-derived factors (pro-inflammatory cytokines and adipokines) [8, 9] impair the vasomotor function of coronary resistance arteries [10–13]. Much less is known the mechanisms regulating the release of these cytokines into the circulation, which enable them to exert their remote effects in the body. Adipose tissue possesses a dense network of microvessels ensuring adequate tissue perfusion [14]. It is known that pro-inflammatory cytokines and adipokines, such as TNF, resistin and IL-6 may cause vascular dysfunction [15], but the nature of their remote effects on coronary microvessels remained poorly described. TNF is released from the cell surface by the action of the disintegrin and metalloproteinase (MMP), TNF converting enzyme (TACE), which is regulated by tissue inhibitor of MMP (TIMP)-3 [16]. Interestingly, recent studies showed that TIMP-3/TACE pathway is involved in the control of glucose homeostasis in adipose tissue, and also induced vascular inflammation in models of obesity in mice [17] as well as in patients with diabetes [18]. Several recent studies set out to elucidate mechanisms that are involved in the release of adipokines into the systemic circulation. This review aims to examine studies that focus on alterations in vasomotor dysfunction of coronary arteries in obesity. A description is also provided about the role of proinflammatory cytokines and adipokines that are actively released from the expanded adipose tissue and that are believed to be responsible for mediating a remote inflammatory response in the heart of obese patients.

## CORONARY MICROVASCULAR DISEASE IN OBESITY

Increase in body mass, muscular or adipose type, requires a higher cardiac output and expanded intravascular volume to meet the elevated metabolic requirement [19]. In

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"uncomplicated" obesity, lack of co-morbid conditions such as hypertension and diabetes, increased left ventricular mass may be appropriate for body size [20]. This is considered to be an early adaptation of cardiac function, which accommodates for the higher hemodynamic and metabolic demand in obesity. Cardiac adaptation also implies changes in the coronary circulation. The question is whether changes in the coronary circulation are able to meet the increased metabolic demand in obesity?

Myocardial blood flow, as measured by positron emission tomography (PET) was significantly reduced in post-menopausal women with obesity [2]. In contrast, pre-menopausal women with similar level of obesity exhibited a higher myocardial blood flow at baseline, when compared to lean subjects, while no difference was detected between lean and obese men [21]. By using cardiac magnetic resonance imaging, neither the resting myocardial blood flow, nor the adenosine-induced hyperemic flow were correlated with obesity in asymptomatic patients in the Multi-Ethnic Study of Atherosclerosis (MESA), which involved 222 men and women [6]. An elevated myocardial blood flow has also been described in postmenopausal obese women without coronary artery disease, however the increase in resting blood flow was associated with a significantly reduced coronary flow reserve [22]. A study by Schindler *et al*. found that while baseline myocardial blood flow did not differ, cold pressor test- or dipyridamole-induced increases in blood flow were significantly reduced in obese patients, when compared to lean individuals [3]. Quercioli *et al*. also found that cold pressor test-induced increase in myocardial blood flow is progressively declined in overweight and obese patients [4]. In another study, coronary flow reserve measured by PET/CT did not differ between control and overweight, whereas it was significantly reduced in obese individuals [5]. Taken together, these studies indicated that while basal myocardial blood flow is not necessary compromised in obese subjects alterations may manifest when the coronary circulation is challenged to mimic the increased metabolic demand in obesity.

The coronary circulation matches blood flow with metabolic requirements by coordinating the vascular resistance in different-sized coronary vessels, which is governed by distinct regulatory mechanisms, such as the myogenic, flow or metabolic control [23, 24]. The large, conduit coronary arteries exert small resistance; resistance to blood flow rises as the vessel diameter decreases in arterioles with a diameter of less than 300 μm. Thus, it seems, it is the response of coronary resistance arteries to pharmacological or physiological stimuli that may be altered in obesity. At present, the impact of obesity on vasomotor regulation of coronary arterioles and the exact underlying mechanisms are not well understood. Coronary arterioles from the heart of obese patients exhibit a reduced endothelium-dependent, bradykinin-induced dilation, however the response is augmented in the simultaneous presence of obesity and hypertension [25]. Oltman *et al*. have investigated the progression of coronary arterial dysfunction in obese Zucker rats and found that coronary arteriolar dilation to acetylcholine (ACh) was preserved in 16–24 week old animals, but dilations became reduced in 28–36 week old rats [26]. Katakam *et al*. reported that in 12-week old obese Zucker rats ACh-induced dilation of small coronary arteries was preserved, although a reduced vasodilation to insulin was also reported in this study [27]. Coronary arterioles from pigs fed a high fat diet to induce obesity exhibited impairment of dilation to bradykinin [28], whereas coronary

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dilation to ACh was preserved in high fat fed, obese rats [29]. More intriguing, Prakash *et al*. have reported that ACh-induced dilation of coronary arterioles in obese Zucker rats is markedly enhanced [30]. Thus it is possible that the dilator function of coronary microvessels declines during the progression of obesity and with its associated diseases. The important question however remains whether changes - maintained or even enhanced - vasodilator function of coronary resistance arteries are able to meet the elevated metabolic demand in obesity. In this context, in dogs with experimental obesity and metabolic syndrome, in spite of unaltered basal and stimulated coronary blood flow rate there is an apparent mismatch between myocardial perfusion and metabolism, as estimated by the rate of oxygen consumption [31, 32]. Collectively, these studies suggest that during the progression of obesity, altered behavior of coronary resistance arteries leads to a mismatch between blood supply and augmented metabolic requirement, which gives rise to coronary microvascular disease (CMD).

## ROLE OF ADIPOKINES IN CONTRIBUTING TO CMD IN OBESITY

Adipose tissue can represent 18% and 24% of body weight in normal men and women, respectively, or as much as 52% and 74% of body weight in obese man and women, respectively [33]. Adipocytes perform an important endocrine function by secreting numerous cytokines, hormones, and bioactive peptides and also have a key impact on skeletal muscle and liver function to regulate energy homeostasis and metabolism [34]. Adipocyte-derived adipokines include adiponectin [35, 36], leptin [35], resistin [37], vascular endothelial growth factor (VEGF) [38] and also pro-inflammatory cytokines, such as TNF [39], IL-1, IL-6 [40] and monocyte chemoattractant protein-1 (MCP-1) [41]. It has been found that obesity is associated with decreased circulating level of adiponectin [36] and increased concentrations of leptin [35], TNF, IL-6 [42], MCP-1 [41]. The underlying mechanisms responsible for these alterations remain elusive in obesity, but recent studies propose a key pathological role for hypoxia inducible factor-1α (HIF-1α) in this process. Insufficient adipose tissue perfusion, as the consequence of its rapid expansion has been suggested to cause local hypoxia, which leads to up-regulation of HIF-1α in adipocytes [43, 44]. HIF-1α is a key regulator of the expression of several adipokines, such as leptin, resistin, vascular endothelial growth factor (VEGF), TNF and IL-6 [44] (Fig. **1**). In order to provid evidence for its important role a previous study has shown that mice with tissue-specific knockout of adipose HIF-1α were protected against diet-induced obesity and metabolic dysfunction [45]. Whereas in transgenic mice with constitutive activation of HIF-1α selectively in adipose tissue initiated fibrosis and local inflammatory response [44]. Further studies are needed to elucidate whether pharmacological inhibitors of HIF-1α may represent a novel therapeutic modalities to prevent obesity and its associated diseases.

It is of particular interest in regard to this thematic review article that protein analysis of conditioned medium of primary human adipocytes identified over 300 proteins, most of which are secreted into the systemic circulation [46]. These adipokines may act locally in a paracrine manner, or can be secreted to exert a systemic effect. These systemic effects involve decreased insulin sensitivity in insulin target cells such as adipocytes, hepatocytes and myocytes [47]. Emerging evidence indicates that many of these adipokines and pro-inflammatory cytokines have direct and remote influence on vasomotor function of coronary

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arterioles in obesity [48]. The impact of various adipokines and pro-inflammatory cytokines on coronary artery disease and vascular function is shown in Table **1**.

## Adiponectin

Adiponectin is believed to have positive impact on vascular function [15]. It also acts as an insulin-sensitizing hormone and its down-regulation is considered to be a potential mechanism whereby obesity causes insulin resistance and diabetes [36]. Adiponectin exists in cells and in serum mainly as trimeric, hexameric and high molecular weight forms, and defect in adiponectin multimerization impairs adiponectin stability and secretion, and are correlated with insulin resistance *in vivo* [49]. The stability and secretion of adiponectin are also regulated at the post-translational modification level via hydroxylation, glycosylation and disulfide bond formation [49]. Impaired multimerization of adiponectin is associated with reduced plasma levels of adiponectin, obesity and insulin resistance [49]. In humans, adiponectin was found to protect the heart from ischemia-reperfusion injury through both AMP kinase- and cyclooxygenase-2-dependent mechanisms [50], however, this capacity is decreased in obesity. Greenstein *et al*. have found that healthy adipose tissue around human small arteries likely secretes adiponectin that causes vasodilation by increasing NO bioavailability [15]. However, adiponectin from perivascular fat in obese subjects with metabolic syndrome seems to lose its dilator effects [15]. Up to date, there are no studies proving the potential influence vasoactive effects of adiponectin in the human coronary microcirculation.

## Leptin

Leptin, a key appetite-regulating hormone primarily acts on hypothalamic neurons to activate catabolic and inhibit anabolic pathway, which can result in weight reduction [51]. Accordingly, lower leptin levels were found to be associated with a higher risk of weight gain in healthy young adults [52]. It is known that β-adrenergic stimulation and also TNF can transiently increase the release of leptin from adipocytes. Higher insulin and cortisol levels can also induce the increase leptin levels, as it has been demonstrated after meals [53]. Hyperinsulinemia and high local cortisol levels up-regulate leptin biosynthesis through post- and pretranscriptional mechanisms [54]. Despite the expected beneficial effects the therapeutic use of leptin has been limited by hypothalamic leptin resistance in obese human [51]. In many obese subjects leptin secretion was found to be significantly higher than in lean subjects, indicating that leptin resistance rather than insufficient leptin production [53]. Thus, pharmacological modulators of leptin receptor sensitivity have been envisioned as promising therapeutic tools.

Interestingly, it has also been posited that in obesity, the altered vasomotor function could arise from the adverse effects of elevated circulating leptin [36]. Knudson *et al*. have found that pathological concentration of leptin (625 pmol/l) attenuated dilation to ACh in coronary arteries of normal dogs, whereas physiological concentrations (250 pmol/l) were without effect [10]. In the study by Payne *et al*., leptin, likely to be released from perivascular adipose tissue, elicited reduction of bradykinin-induced coronary relaxation in a swine model of metabolic syndrome; a response, which was mediated by activation of protein kinase C (PKC) [55]. In cultured human umbilical endothelial cells, increased concentration

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of leptin was associated with increased endothelial NO synthase (eNOS) expression, but also decreased intracellular L-arginine levels, resulting in eNOS uncoupling and consequent eNOS-derived superoxide and peroxynitrite production [56]. Somewhat contradictory, Schindler *et al*. showed that elevated plasma leptin levels in obese patients exert beneficial effects on the coronary endothelium [57]. Although higher leptin concentrations were associated with impaired arterial distensibility in healthy adolescents [58], acute subcutaneous administration of leptin unexpectedly increased flow-mediated dilation of brachial artery [59]. Furthermore, in obese women, leptin concentration did not predict impaired flow-mediated brachial artery dilation [60]. Thus, the overall impact of adipocyte-derived leptin in contributing to the development of coronary artery dysfunction remains elusive in obesity.

## Resistin

Resistin is another adipokine critically involved in metabolic homeostasis. It was found that in adipocytes, leptin and resistin are compartmentalized into different secretory vesicles, whose secretion are oppositely regulated by insulin/glycolytic substrates as well as by the cellular level of cAMP and protein kinase A [61]. The resistin gene is expressed almost exclusively in adipocytes and resistin level has shown to be elevated in obese patients. Insulin and TNF shown to down-regulate resistin expression, whereas glucose and glucocorticoids seem to play important role in its induction [62]. Elevated plasma resistin is correlated with levels of inflammatory markers, including soluble TNF receptor-2, IL-6, and lipoprotein-associated phospholipase A2 along with increased coronary calcium score – a measure of the severity of coronary sclerosis – in 879 asymptomatic subjects [63]. Similar correlation was found in patients with symptomatic coronary artery disease [64]. Furthermore, serum resistin level was found to be independent predictor of major adverse cardiovascular events in patients undergoing percutaneous coronary intervention [65]. To provide experimental evidence for the direct vascular effect of resistin, porcine coronary arteries were exposed to exogenous resistin *in vitro*, which resulted in a reduced dilation to bradykinin, via increasing of vascular reactive oxygen species (ROS) production [11]. Similarly, Dick *et al*. have found a reduced bradykinin-induced dilation of canine coronary arteries exposed to resistin; an effect which was, however, independent from increased ROS production and was not affected by endothelial production of NO or proctacyclin [12]. In their study of human saphenous vein endothelial cells, Verma *et al*. demonstrated that resistin increased expression of endothelin-1 [66]. Endothelin-1 is a potent vasoconstrictor and it is also an important mediator of enhanced ROS production in the vasculature. Over-expression of resistin leads to increased NAD(P)H oxidase activity via increasing the levels of NOX2, NOX4, and p47phox in the rat heart, and results in marked 3-nitrotyrosine formation [67]. Decreased eNOS levels were also observed in human coronary artery endothelial cells incubated with resistin [57]. The authors also demonstrated resistin's ability to impair mitochondrial respiratory chain function implicating the mitochondria as a key source of ROS production induced by resistin exposure [57].

Taken together, several recent studies indicate that adipokines, such as adiponectin, resistin, and leptin exert direct, detrimental effects on coronary arteriolar dilator function in obesity. These effects, in part, are mediated by loss of NO and enhanced ROS production in coronary

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arteries of obese subjects. The exact mechanisms by which various adipokines increase vascular ROS production are not entirely understood; it can be mediated either indirectly by agonist such as endothelin-1 [66] and angiotensin II [68] or could be attributed to direct, receptor-mediated activation of various signaling pathways in endothelial and smooth muscle cells, such as JNK, NFκB or PKC [55, 69].

## SOURCE(S) AND RELEASE OF TNF FROM ADIPOSE TISSUE

TNF is one of the most important mediators playing a role in the development of endothelial dysfunction in obesity [70–72]. It has been shown that TNF is secreted by adipocytes [73] and its expression in adipose tissue is increased in obesity [72, 74], which correlates with the severity of insulin resistance [75, 76]. It has been found that obese individuals express 2.5-fold higher TNF in adipose tissue relative to lean controls [75]. TNF may elicit a direct vasoconstrictor [77, 78] or vasodilator effects depending on the vascular bed studied [79–81]. While TNF-mediated constriction in coronary or bronchial arteries is mediated by endothelial release of endothelin-1 [77, 78], vasorelaxation in cerebral or brachial arteries involves NO and dilator prostaglandin production [79, 80]. NAD(P)H oxidase-dependent $H_2O_2$ production and subsequent activation of calcium-activated potassium channels has also been implicated in TNF-induced vasorelaxation [82]. Recent reports provide evidence that TNF inhibits endothelium-dependent, NO-mediated dilation of coronary arterioles, interferes with ceramide-induced activation of Jun N-terminal kinases (JNK), and leads to subsequent production of superoxide anion [71]. Moreover, TNF via increasing NAD(P)H oxidase-derived ROS production has been implicated in the development of coronary arterial dysfunction in obese Zucker rats [13]. Tesauro *et al*. have shown that TNF neutralizing antibody, infliximab, ameliorated the blunted vascular reactivity in obese patients, likely via reducing oxidative stress [83]. Thus, evidence indicates that TNF plays a crucial role in the development of coronary microvascular dysfunction in obesity and studies also provided rational for therapeutic intervention, such as the use of TNF neutralizing antibody in cardiovascular prevention.

Emerging evidence indicate a crucial role for mechanisms regulating TNF secretion from adipose tissue contributing to the development of various pathologies associated with obesity. TNF release from human adipose tissue and cultured adipocytes occurs at low levels under control conditions, which is increased substantially in response to LPS stimulation [84]. In obesity, adipose tissue is infiltrated with large number of macrophages [85, 86] that can comprise up to 40% of the cells within adipose tissue [86]. Baker *et al*. reported increased macrophage infiltration in epicardial adipose tissue when compared to abdominal adipose tissue [87]. Adipose tissue macrophages were shown to contribute to the substantial release of TNF and IL-6 [86]. More recently, Weisberg *et al*. reported that although differentiated white adipocytes are capable of producing TNF, macrophages from the stromal vascular fraction of adipose tissue are the primary source of adipose tissue-derived TNF. The authors proposed M1 macrophages as the main source of increased TNF production in obesity [86].

How the release of TNF from adipocytes and macrophages is regulated in obesity still remains poorly understood. TNF is synthesized as a 26 kDa transmembrane protein that

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undergoes cleavage by TNF converting enzyme (TACE, also known as a disintegrin and metalloproteinase-17 (ADAM17)) and is released into the circulation as a soluble, 17 kDa TNF molecule [88, 89]. The cleavage of such membrane bound TNF is a highly regulated process. TACE is naturally inhibited *in vivo* by tissue inhibitor of matrix metalloproteinase-3 (TIMP3), which binds to the catalytic domain of the enzyme. The balance between TACE and TIMP3 activities seems to determine serum TNF levels, and a reduction of TIMP3 expression results in an elevation of serum TNF due to unrestricted TACE activity [90]. TACE can undergo several posttranslational modifications (it has several glycosylation and phosphorylation sites), however little is known about its regulation in obesity. At an early stage of the development of obesity, TACE activity seems to be elevated in visceral adipose tissue, but not in liver or skeletal muscle. Interestingly, intraperitoneal injection of exogenous TNF increased TACE activity and protein expression in white adipose tissue of mice [91]. Treatment with the TACE-inhibitor marimastat improved surrogate markers for insulin sensitivity and reversed steatosis in mouse model of diet-induced obesity and leptin deficiency [92]. Adipose tissue from high fat-fed mice exhibited an increase in TACE expression, when compared to control diet fed mice [93]. Whether changes in adipose tissue (adipocyte versus macrophage) TACE activity and consequent release of TNF into the systemic circulation contributes to the development of coronary vasomotor dysfunction in obesity has yet to be elucidated.

## SUMMARY

Adipose tissue possesses a dense network of microvessels ensuring sufficient exchange of nutrients and oxygen. The adipose tissue vasculature delivers lipids to their storage depot in the adipocytes and also exports nutrients in response to metabolic need. It is the view that adipokines and other vasoactive mediators are secreted from adipocytes and other cellular elements from the adipose tissue, such as macrophages, and via the adipose tissue microvascular network are delivered into bloodstream to exert their remote effects. In obesity, insufficient adipose tissue perfusion may result in local hypoxia, which increases the levels of hypoxia inducible factor, HIF-1α in adipocytes [43, 44]. HIF-1α may lead to increased synthesis of various inflammatory adipokines, including TNF, IL-6, leptin and resistin [44] (Fig. **1**). Emerging evidence indicates that cellular mechanisms regulating the controlled release of various adipokines and proinflammatory cytokines from the adipose tissue are the major determinants of remote coronary microvascular inflammation in obesity and may represent new therapeutic targets for therapeutic intervention.

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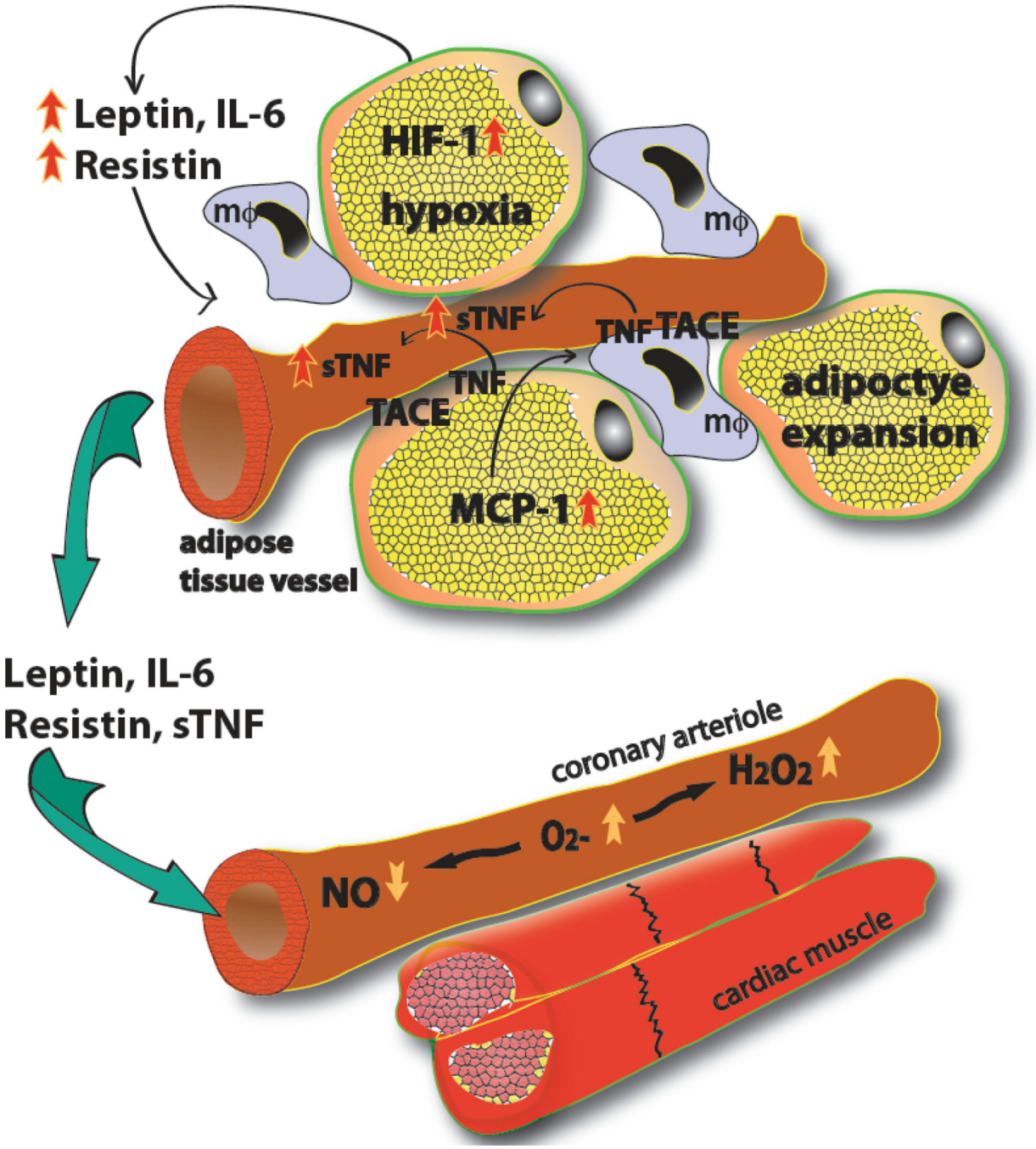


**Fig. (1). Adipose tissue-derived cytokines and coronary microvascular vasomotor dysfunction**

In obesity, expansion of adipose tissue leads to tissue hypoxia, which via hypoxia inducible factor-1α (HIF-1) results in an increased production of leptin, resistin, TNF, and IL-6. Adipocytes also enhance monocyte chemotactic protein-1 (MCP-1) synthesis, which facilitates macrophage (mΦ) accumulation in adipose tissue. TNF is cleaved by TACE from the cell membrane of adipocytes and macrophages leading to substantial release of soluble form of TNF (sTNF). The secreted adipokines and pro-inflammatory cytokines then reach the coronary microcirculation to exert their remote effects, via inducing production of

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superoxide anion ($O_2^{-\cdot}$) and hydrogen peroxide ($H_2O_2$) in the coronary arteriolar wall, which leads to reduced availability of NO, hence limited vasodilator function.

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## Table 1

Studies evaluating the vascular impact of various adipokines and pro-inflammatory cytokines in animal models and in human with obesity.

| | Level in Obesity | Association with CAD | *In vitro* Effect on Coronary Circulation of Animal Models | *In vivo* Effect in Humans |
|---|---|---|---|---|
| **leptin** | Increased [94] | Independent risk factor for CAD [95]<br>Predictor of future cardiovascular events in CAD patients [96]<br>Strongly predicts first-ever AMI [97] | Blunted response to ACh in canine coronary artery [10]<br>Exacerbates coronary endothelial dysfunction in swine [55] | NO-independent vasodilation in forearm [98]<br>No significant correlation with NO-mediated FBF [99]<br>Positive correlation with MBF [3] |
| **adiponectin** | Decreased [36] | Lower plasma levels in patients with CAD [100–102]<br>High plasma levels associated with lower risk of AMI [103] | Restores ACh-induced vasodilation in leptin receptor deficient mice [104] | Decreased FBF in hypoadiponectinemia [105] |
| **resistin** | Increased [106] | Associated with the severity of CAD [64] | Impairs canine coronary dilation to bradykinin [12]<br>Reduces vasorelaxation in swine coronary arteries [11] | Negative correlation with FMD [107, 108] |
| **TNF** | Increased [109–111] | Elevated after AMI [112]<br>G-308A gene polymorphism associated with CAD [113] | Coronary constriction through endothelin-1 [77, 78]<br>Endothelial dysfunction of coronary arterioles [13–117] | Increased TNF correlated with FBF [118]<br>Anti-TNF improves FMD [119]<br>Intra-arterial TNF impairs bradykinin- and ACh-induced vasodilatation [120] |
| **IL-6** | Increased level [121]<br>Reduced level after weight loss [122] | Increased risk of CAD [123, 124],<br>Predict vascular events in postmenopausal women [125] | Overexpression of IL-6 impairs EDHF-mediated dilation in coronary arterioles [126] | No effect [127], independently related to impaired FMD [128] |

CAD: coronary artery disease, AMI: acute myocardial infarction, FBF: forearm blood flow, MBF: myocardial blood flow, FMD: flow mediated dilation, EDHF: endothelium-dependent hyperpolarizing factor.