

Metalloproteinases in the pathogenesis and progression of metabolic syndrome: potential targets for improved outcomes

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Abstract: Matrix metalloproteinases (MMPs) constitute a family of more than 25 calcium-dependent, zinc-containing endopeptidases, synthesized by multiple cell types. These enzymes play an important role during physiological tissue development and remodeling and angiogenesis, as well as in pathophysiological conditions such as obesity and atherosclerotic process. Moreover, circulating levels of MMPs have emerged as potential biomarkers of cardiovascular disease. MMPs are regulated by different factors such as insulin resistance and obesity. Different components of the metabolic syndrome have been identified as possible stimulus for the synthesis and activity of MMPs. On the other hand, pro-inflammatory and anti-inflammatory cytokines, such as leptin and adiponectin, respectively, are associated with the regulation of MMPs. Leptin induces expression of MMP-2 activators as well as expression of MMP-2, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-1 in different human cells. Adiponectin may play a protective role in plaque rupture through selectively increasing TIMP expression. The hepatic manifestation of metabolic syndrome is nonalcoholic fatty liver disease (NAFLD). MMPs may remodel the liver parenchyma during the process of liver fibrosis. MMP-2 and MT1-MMP have been considered to be fibrogenic enzymes. There are few studies analyzing the role of MMPs in NAFLD, and most of them include study on mRNA expression, but even the results on their expression pattern remains controversial. MMPs could be considered as possible therapeutic targets. Different studies demonstrated that metformin, thiazolidinediones, and antibiotics could have inhibitory effects on the expression of MMPs; however, a rational study of lifestyle modifications as well as further studies of pharmacological therapies that influence MMPs are necessary to generate the information that physicians will probably need to improve the treatment of patients. The aim of this revision is to update the data about MMPs in the pathogenesis and progression of metabolic syndrome and the possible effect of different drugs on the behavior of these enzymes.

Keywords: metalloproteinases, metabolic syndrome, insulin resistance, nonalcoholic fatty liver, metformin, thiazolidinediones

Introduction

Matrix metalloproteinases (MMPs) constitute a family of more than 25 calcium-dependent, zinc-containing endopeptidases, synthesized by multiple cell types.¹ These enzymes present proteolytic function involved in the degradation of the components of extracellular matrix (ECM) and basement membranes (BMs), such as collagens, proteoglycans, elastin, laminin, fibronectin, and other glycoproteins.² They can be classified according to their substrate specificity as collagenases, stromelysins, matrilysins, gelatinases, and membrane-type metalloproteinases.³

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Most MMPs are secreted as precursor zymogens that are activated through a proteolytic process. Under physiological conditions, the activity of MMPs is regulated at the transcription level through interaction with specific ECM components and by inhibition of endogenous tissue inhibitors of MMPs (TIMPs).^{4,5} Consequently, the balance between activated MMPs and TIMPs locally determines the net result of the activity of MMPs in tissues.

MMPs play an important role during physiological tissue remodeling in embryonic development⁶ and angiogenesis,⁷ as well as in pathophysiological conditions such as atherosclerotic plaque development, and vulnerability⁸ and obesity.⁹ MMPs are known to be expressed in physiological conditions at some baseline level, but are differentially expressed in response to certain hormones, growth factors, and cytokines.¹⁰

Different studies have shown that increased levels of gelatinases (MMP-2 and MMP-9) are expressed in fatty streaks and atherosclerotic plaques, being partially responsible for plaques vulnerability.^{11,12} Regarding obesity, several MMPs have been studied in reference to the development of adipose tissue. Recent studies show that gelatinases are secreted by adipose tissue and that their activity is modulated during adipose tissue expansion/regression.¹³⁻¹⁵

Metabolic syndrome

Metabolic syndrome (MS) is a cluster of risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). According to the most used definition, the revised Adult Treatment Panel-III,¹⁶ MS is diagnosed when at least three of five of the following alterations are present: visceral obesity (waist circumference >102 cm in men or >88 cm in women); raised arterial blood pressure (>130/85 mmHg); dysglycemia (fasting plasma glucose >100 mg/dL); raised triglyceride concentrations (\geq 150 mg/dL); low high-density lipoprotein cholesterol (HDL-cholesterol <40 mg/dL in men or <50 mg/dL in women). MS confers a fivefold increase in the risk of T2DM and twofold increase in the risk of developing CVD over the next 5 to 10 years.¹⁷ Moreover, patients with MS are at two- to fourfold increased risk of developing a stroke, three- to fourfold increased risk of developing a myocardial infarction, and twofold increased risk of dying from such an event compared with those without the syndrome,¹⁸ regardless of a previous history of cardiovascular events.¹⁹ The pathophysiology of MS is very complex and not yet clear. Moreover, MS is associated with other systemic complications, such as obesity and fatty liver disease that affect different organs and organ systems. The expansion of adipose

tissue is related to systemic inflammation through the secretion of adipokines in the systemic circulation resulting in a chronic inflammatory state, characteristic of MS.

MMPs and MS

Alterations of the arterial vasculature, especially of the endothelium, and basal membrane are characteristics of MS; other features associated with MS include polymorphonuclear activation, increased oxidative stress, and changes in the expression of MMPs.²⁰ Different components of MS have been identified as possible stimuli for the synthesis and activity of MMPs.¹⁰ Hoseini et al found strong associations of MMP-8 with components of MS, suggesting that this MMP would be a potential cardiometabolic risk marker for MS, possibly through dependent and independent mechanisms of chronic low-grade inflammation.²¹ In our laboratory, we found increased MMP-2 plasma activity in women with MS,²² which correlates with vascular cell adhesion molecules involved in the plaque development.²³ In accordance with the results obtained in other studies, Hopps et al showed an increase in plasma concentrations of MMP-2 and MMP-9 and their inhibitors (TIMP-1 and TIMP-2) in diabetic and nondiabetic subjects with MS.²⁴ However, other authors found an increase in pro-MMP-9 and TIMP-1 levels, which are associated with raised concentrations of inflammatory markers and adhesion molecules, without differences in MMP-2 and TIMP-2 values in comparison with healthy controls.²⁵ The different stages of the CVD could be a main factor in conditioning the circulating levels of MMPs. In a study by Miksztowicz et al, the patients included in the study were women with MS but without clinical evidence of unstable plaques.²² The increased MMP-2 activity could be associated with the first steps of the atherogenic process mainly related to the vascular smooth muscle cells (VSMCs) migration and intimal thickening.²⁶ The lack of MMP-9 detection could be attributed to the fact that this MMP is reported to be associated mainly with the plaque rupture in advanced lesions.¹¹ In turn, Opstad et al have shown that the MMP-9 21562 C/T polymorphism modified the risk of new clinical events in patients with MS, partly mediated through altered MMP-9 regulation. Moreover, in patients with MS, the MMP-9 T-allele was associated with significantly increased risk of cardiovascular events and higher MMP-9 circulating levels, compared with non-MS patients.²⁷

It is important to take into account that adipose tissue expansion could contribute to the circulating levels of MMPs, questioning the role of these enzymes as CVD biomarkers. In human adipose tissue from men with MS, a lack of

association between adipose tissue mRNA and plasma levels of MMP-9 has been reported, suggesting that this tissue is not a major contributor to circulating MMP-9.²⁸

In obesity, the expansion of adipose tissue is associated with modifications involving adipogenesis, angiogenesis, and ECM remodeling. MMPs are involved in the control of proteolysis and adipogenesis during obesity-mediated fat mass development (Figure 1),²⁹ either through the degradation of ECM and BM components or by the activation of latent growth factors.¹⁴ Maquoi et al reported an upregulation of mRNA levels of some MMPs and TIMPs (MMP-3, MMP-11, MMP-12, MMP-13, and MMP-14 and TIMP-1) and downregulation of others (MMP-7, MMP-9, MMP-16, and MMP-24 and TIMP-4) in adipose tissue from lean and obese mice.³⁰ These modulations differed according to the origin of the adipose tissue (gonadal vs subcutaneous), supporting the concept that different localization of fat deposits presents a different metabolic behavior.³¹

Through in vitro studies, Lijnen et al proposed that MMP-2 has a functional role in early and later stages of adipocyte differentiation,³² suggesting a possible function of MMP-2 in adipogenesis in vivo. On the contrary, in an in vivo animal model of insulin resistance induced by sucrose-rich

diet, MMP-2 and MMP-9 activity was decreased in the visceral adipose tissue; however, this was not associated with changes in the activity of MMPs in plasma.³³ The lack of association between adipose tissue and plasma activity of the gelatinases suggests that this tissue is not a major contributor of the circulating enzymes. In accordance with these results, Van Hul et al found that MMP-9 does not seem to play a major role in the adipose tissue development in murine models of diet-induced obesity.¹⁵ On the other hand, knockout models of different MMPs, such as MMP-19-null, MMP-3-null, or MMP-11-null mice, are associated with increase in adipose tissue development when mice are fed a high-fat diet.³⁴⁻³⁶ In contrast, in membrane type 1 MMP knockout model, visceral adipose tissue development is aborted, leaving tissues populated by mini-adipocytes which render null mice lipodystrophic.³⁷ These controversies could be associated with not only the model used but also the stage of adipose tissue development.

Effect of insulin resistance on MMP

Insulin resistance causes hyperinsulinemia; therefore, practically all obese individuals, whether diabetic or not, are chronically hyperinsulinemic. Prospective studies found that

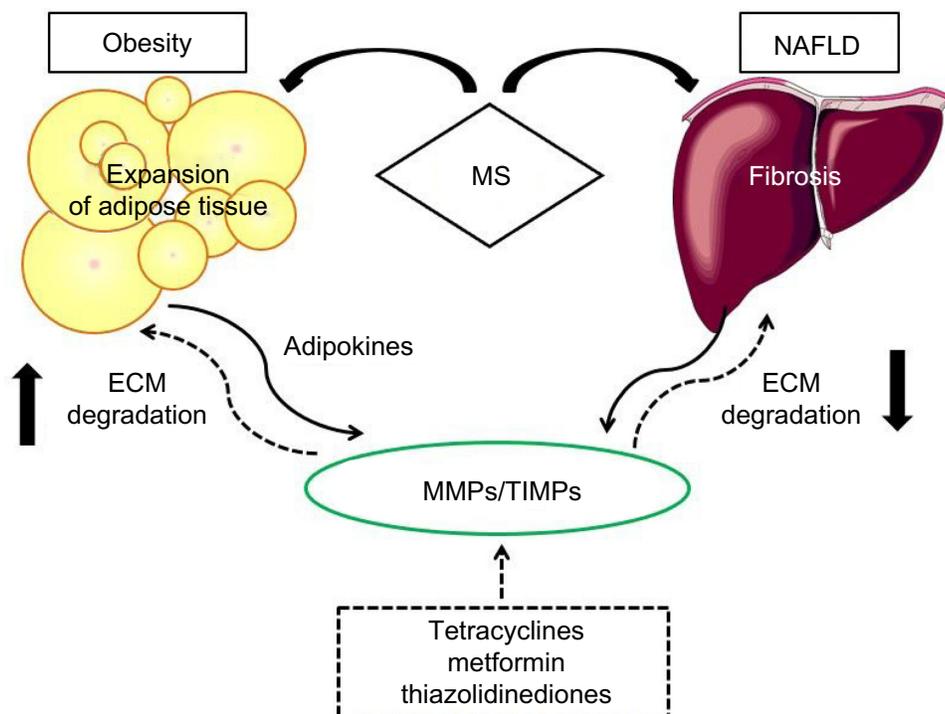


Figure 1 Relationship between MS, obesity and NAFLD, and MMPs/TIMPs balance.

Notes: MS is characterized by abdominal obesity and NAFLD. During the expansion of adipose tissue, there is an increase in the secretion of adipokines leading to an imbalance in MMP/TIMPs, which in turn promotes ECM degradation. In NAFLD, the increased expression of TIMPs and concomitantly the reduced activity of MMPs result in protein accumulation in the extracellular space and fibrosis. There is an evidence of the effect of tetracyclines, metformin, and thiazolidinediones on the activity of MMPs and TIMPs.

Abbreviations: MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; MMPs, matrix metalloproteinases; TIMP, tissue inhibitor of metalloproteinase; ECM, extracellular matrix.

elevated insulin levels were associated with an increased risk for ischemic heart disease, particularly in men,^{38,39} independent of the known CVD risk factors.

Early reports implicated insulin or insulin-like growth factor-1 signaling through the PI3K/Akt cascade as being responsible for the stimulation of MMP activity.^{40,41} In vascular tissues, this pathway controls the metabolic actions of insulin, including glucose and amino acid uptake, glycogen synthesis, and nitric oxide (NO) production,⁴² and is inhibited by free fatty acids in major insulin target tissues.⁴³ Different studies have shown that insulin regulates MMPs in different ways according to the organ. Boden et al observed in rat aorta that free fatty acids and insulin promote the activation of MMP-2, MMP-9, and MT1-MMP through the stimulation of pro-inflammatory cytokines production.⁴⁴ In contrast, in the liver, hyperinsulinemia promotes a decrease in MMP-2, MMP-9, and MT1-MMP levels.⁴⁵

It has been shown that the expanded adipose tissue, characteristic of insulin-resistant state, presents areas of relative hypoxia.⁴⁶ The development of hypoxia within white fat underlies the establishment of the inflammatory response in the tissue that leads to the diseases associated with obesity. Hypoxia-induced changes in adipokine production, having local effects, such as inflammation, or affecting other tissues, are associated with changes in the circulating level of the key adipocyte hormones leptin and adiponectin, as well as MMP-2.⁴⁶

Effects of cytokines on MMPs

Leptin and adiponectin are the main cytokines synthesized in adipose tissue and exhibit different functions and opposing effects on inflammation and the atherosclerotic process.⁴⁷

Leptin

Leptin was the first adipocytokine discovered in 1994, and its levels are increased in the plasma of obese individuals. Leptin shows central and peripheral effects. Central effects include the regulation of food intake and energy expenditure.⁴⁸ Leptin also mediates a wide array of direct peripheral effects, including those specific to the cardiovascular system, given that its receptors are also present in many peripheral tissues. In vitro, leptin exhibits different proatherogenic effects, such as endothelial and VSMCs activation, migration, and proliferation.^{49,50} Leptin plays an important role in ECM remodeling by regulating the expression of MMPs and TIMPs. Previous studies in vitro have demonstrated stimulation of proteolytic activity of MMPs by leptin.^{51,52} It has been reported that exposure of myofibroblasts to leptin

significantly increased the expression of MT1-MMP, resulting in an increase of MMP-2 activity, without changes in protein levels.⁵³ Park et al reported that leptin induces elevation of MMP-2, MMP-9, and TIMP-1 expression in human umbilical vein endothelial cells and in human coronary artery smooth muscle cells⁴⁹ through the generation of intracellular reactive oxidative species. In reference to adipose tissue, in vitro studies have demonstrated that MMP-2 secretion was significantly promoted by leptin treatment in 3T3-L1 preadipocytes.⁵⁴ Because plasma leptin concentrations are associated with obesity and type 2 diabetes,⁵⁵ leptin signaling may represent a therapeutic target for the prevention of obesity and CVD.

Adiponectin

Adiponectin is the most abundantly secreted adipokine in physiological situations, and its levels are inversely associated with obesity and inflammation.⁵⁶ Adiponectin exerts well-known insulin-sensitizing effects and is also reported to possess beneficial effects on vascular function and may exhibit antiatherogenic and anti-inflammatory effects. The pathway by which adiponectin affects vascular function has been evaluated through in vitro experiments in endothelial cells from human aortas. Adiponectin increases NO production and/or ameliorates oxidized low-density lipoprotein (oxLDL)-induced suppression of endothelial NO synthase activity.⁵⁷ Furthermore, adiponectin has been shown to affect atherosclerotic plaque formation and stability.⁵⁶ Adiponectin suppresses lipid accumulation and class A scavenger receptor expression in macrophages, resulting in markedly decreased uptake of oxLDL and inhibition of foam cell formation.⁵⁷ It also binds to platelet-derived growth factor-BB and sub-endothelial collagens and suppresses the proliferation and migration of human aortic smooth muscle cells.⁵⁸

In vitro studies have shown that adiponectin exhibits different effects on the expression of different MMPs. Tong et al showed that adiponectin increased the secretion of MMP-3 in cultured human chondrocytes,⁵⁹ whereas this cytokine reduced MMP-2 and MMP-9 protein levels of endometrial cancer cells.

Adiponectin may also play a protective role in plaque rupture through selectively increasing TIMP expression and secretion in human monocyte-derived macrophages. This effect is mediated via the ability of adiponectin to increase the expression and secretion of interleukin-10 (IL-10), a TIMP-inducing cytokine.⁶⁰

Studies in humans show that in patients with combined hyperlipidemia, adiponectin decreased MMP-2, MMP-9,

TIMP-1, and TIMP-2 plasma levels.⁶¹ In accordance with these results, in our laboratory we observed an inverse association between plasma adiponectin levels and circulating activity of MMP-2 in patients with MS, independently of obesity markers, suggesting that the inflammatory process associated with highest CVD risk would be involved in MMPs vascular production.⁶²

Hypoadiponectinemia has been proposed to contribute to increased activity of MMP-2 in obese/hypertensive children and adolescents.⁶³ Moreover, in patients with acute coronary syndrome, a negative relationship between adiponectin and MMP-9/TIMP-1 ratio has been described; this ratio is considered an independent predictor of atherosclerotic plaque stability and severity of coronary atherosclerosis.⁶⁴ However, no correlations have been observed between adiponectin and plasma levels of MMP-1 in coronary patients.⁶⁵ As has been mentioned previously, this could be a consequence of the behavior of MMPs according to cardiometabolic risk environments.

MMPs and NAFLD

NAFLD is defined as an excessive accumulation of triglycerides in the liver (>5% of hepatocytes histologically) in the absence of alcohol excess.⁶⁶ NAFLD comprises a morphological spectrum of liver lesions ranging from simple triglyceride accumulation in hepatocytes (hepatic steatosis [HS]) to inflammatory and hepatocellular ballooning injury (nonalcoholic steatohepatitis [NASH]), eventually leading to fibrosis and cirrhosis.⁶⁶

NAFLD is the leading cause of liver diseases in Western countries.⁶⁷ The prevalence is increasing because of the rising occurrence of obesity and T2DM;⁶⁶ in fact, NAFLD is considered as the hepatic manifestation of MS.⁶⁸ NAFLD is present in 10%–24% of the general population in various countries, while the prevalence of NAFLD in obesity is 30% to 100% and in T2DM is 10% to 75%.⁶⁹

In healthy liver, homeostasis of ECM is sustained by a precisely regulated permanent turnover directed by MMPs and TIMPs. Hepatic stellate cells (HSCs), localized in the perisinusoidal space, are the most important producers of ECM.⁷⁰ Upon chronic damage to liver tissue, HSCs become activated and differentiate into a fibroblast-like phenotype, increasing deposition of ECM. Therefore, expression of MMPs may vary during the progression of fibrotic liver disease (Figure 1).⁶⁶

The activated HSCs produce very important cytokines, growth factors and inflammatory mediators, adhesion molecules (I-CAM-1, V-CAM-1, N-CAM), MMPs (MMP-1, -2,

-3, -14), and protease inhibitors (TIMP-1, -2, plasminogen activator inhibitor-1), among other proteins.⁷⁰ It has been reported that activated HSCs present increased expression of TIMP-1 and concomitantly reduced activity of MMPs with the subsequent protein accumulation, especially collagen type I, III, and IV, in the extracellular space.⁷¹ In murine models of cirrhosis and NASH, it has been reported the increase of expression and activity of MMP-2 and -9, respectively.^{72,73} HSCs secrete MMP-2 and MT1-MMP; the level of MMP-2 expression increases during the process of experimental hepatic fibrosis as well as during the process of hepatic fibrosis in chronic hepatitis, and it decreases during the process of cirrhosis.⁷⁴ These MMPs may remodel the liver parenchyma during the process of liver fibrosis. Both MMP-2 and MT1-MMP have been considered to be fibrogenic enzymes because MMP-2 expression is stimulated by TGF- β while MMP-1 expression is downregulated by TGF- β .⁷⁵ Meanwhile, in human liver biopsies, no difference in MMP-9 activity was observed in steatosis situations.⁷³ Anyway, there are few studies analyzing the role of MMPs in NAFLD, and most of them study mRNA expression, but even the results on their expression pattern remains controversial.

MMPs as possible therapeutic targets

Metformin and thiazolidinediones

Metformin is a commonly prescribed oral anti-hyperglycemic drug used in the management of T2DM. Recent evidence indicates that metformin shows significant effects on tumorigenesis and cancer cell growth, and also exhibits antioxidant effects. It has been reported that patients with T2DM who take metformin have a lower risk of cancer than those who do not take metformin.^{76,77}

Given the effect of metformin on tumorigenesis, special attention has been given to its effects on MMPs. Inhibitory action of metformin, a pharmacological activator of AMPK, on the MMP expression has been described in human fibrosarcoma cells. Hwang et al showed that metformin inhibits MMP-9 expression in human fibrosarcoma HT-1080 cells.⁷⁸ Besides, Esfahanian et al have studied the effect of metformin on human umbilical vein endothelial cells, an established model for angiogenesis study.⁷⁹ They observed that metformin significantly decreased MMP-2 and MMP-9 mRNA levels in a concentration-dependent manner.⁷⁹ Furthermore, it has been demonstrated that metformin reduces MMP-2 expression in human aortic smooth muscle cells, which has been previously induced by leptin.^{49,51} Studies in animals showed that the combined effect of metformin and

gemfibrozil reduces MMP-9 and increases adiponectin and IL-10 levels in streptozotocin-induced diabetes.⁸⁰

Studies in humans have shown controversial results. In two different studies, it has been reported that metformin had no significant effect on serum MMP-9 levels after 3 and 6 months of treatment.^{81,82} However, Kiyici et al showed significant reductions in MMP-9 levels after 52 weeks of treatment, proposing that the beneficial effect of metformin on MMP-9 may result either from direct effects on endothelial cells or indirect actions such as improving glycemic control, promoting weight loss, and lowering the plasma levels of toxic compounds, such as glucose and free fatty acids, transported to the endothelium.⁸³ All these studies included a reduced number of patients with T2MD; more recently, in a double blind, randomized, multicenter study with a similar number of patients, Hanefeld et al proposed that addition of pioglitazone but not of metformin reduces MMP-9 levels.⁸⁴

Blaschke et al revised the effect of different thiazolidinediones, agonists to the peroxisome proliferators-activated receptor γ , and reported inhibition of MMP-9 expression and activity by rosiglitazone and troglizatonone independent of their antidiabetic action.⁸⁵

Pfützner et al showed that pioglitazone downregulated the activated state of peripheral monocytes/macrophages as assessed by mRNA expression of NF κ B and NF κ B-modulated cytokines and decreased plasma levels of MMP-9 independent of glycemic control.⁸⁶ Different studies accord that pioglitazone is able to effectively suppress the expression of MMP-9 via a transcriptional mechanism;^{86,87} however, a recent meta-analysis of more than 700 patients revealed that neither rosiglitazone nor pioglitazone had marked effects on MMP-9 concentrations.⁸⁸

Antibiotics

The tetracyclines belong to a family of broad-spectrum antibiotics that inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site.⁸⁹ Besides, they present non-antimicrobial properties such as the ability to inhibit members of the MMP family (Figure 1). Although many synthetic compounds with the ability to inhibit MMP activity have entered clinical trials,⁹⁰ none progressed to Phase III clinical trials. Doxycycline and minocycline are the most important semisynthetic tetracyclines used clinically as antibiotics. The mechanism by which tetracyclines inhibit MMPs has not been completely elucidated. A proposed mechanism is the direct inhibition of MMPs by the chelation of structural metals within the MMP.⁸⁹

After myocardial infarction, MMP activity is upregulated, suggesting an important role in mediating the acute injury and healing processes of the heart. However, early activation of MMP could also lead to early damage of the cardiac ECM. After ischemia reperfusion injury, MMP-2 activity increases in isolated, perfused rat hearts resulting in proteolysis of troponin I and myosin light chain.^{91,92} The treatment with doxycycline attenuated the increase in MMP-2 activity upon reperfusion and improved the recovery of contractile function.^{93,94} Inhibition of MMP activity holds promise for preserving cardiac structure and function post-myocardial infarction, however, important being the timing of this inhibition. Significant anti-remodeling (ie, beneficial) effects can be observed in the infarcted heart when doxycycline is given for a limited period of time after injury.⁹⁵

Conclusion

As we have reviewed, there is a bidirectional interaction between insulin resistance, a characteristic feature of MS that through different signaling pathways increases the production and activation of MMPs, and MMPs contributing to the development and expansion of adipose tissue with an increase in insulin-resistant state. Other signaling pathways, such as elevated leptin and decreased adiponectin production, also participate in the misbalance between MMPs and TIMPs. The synergistic interaction among these risk factors contributes to the development of heart disease. Given the proved role of MMPs on atherosclerotic plaque vulnerability, a tangled web of different risk factors appears to play a role in accelerating CVD. Pharmacological treatment has started to provide new and promising results for the treatment of MS. Further studies regarding lifestyle modifications as well as pharmacological therapies are necessary to improve the treatment of patients.

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Disclosure

The authors report no conflicts of interest in this work.

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