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Invited critical review

Metalloproteinases in metabolic syndrome ☆

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ABSTRACT

Experimental and clinical evidence supports the concept that metalloproteinases (MMPs), beyond different physiologic functions, also play a role in the development and rupture of the atherosclerotic plaque. Interest in MMPs has been rapidly increasing during the last years, especially as they have been proposed as biomarkers of vulnerable plaques. Different components of the metabolic syndrome (MS) have been identified as possible stimulus for the synthesis and activity of MMPs, like pro-inflammatory and pro-oxidant state, hyperglycemia, hypertension and dyslipidemia. On the other hand, anti-inflammatory cytokines like adiponectin are inversely associated with MMPs. Among the several MMPs studied, collagenases (MMP-1 and MMP-8) and gelatinases (MMP-2 and MMP-9) are the most associated with MS. Our aim was to summarize and discuss the relation between different components of the MS on MMPs, as well as the effect of the cluster of the metabolic alterations itself. It also highlights the necessity of further studies, in both animals and humans, to elucidate the function of novel MMPs identified, as well as the role of the known enzymes in different steps of metabolic diseases. Understanding the mechanisms of MS impact on MMPs and *vice versa* is an interesting area of research that will positively enhance our understanding of the complexity of MS and atherosclerosis.
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Contents

1. Introduction

Metabolic syndrome (MS) is a clustering of risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D). These factors include hyperglycemia, raised blood pressure, dyslipidemia – mainly represented by elevated triglyceride and low HDL-cholesterol – and obesity (particularly with abdominal localization). Patients with MS are twice as likely to be at risk of developing CVD over the next 5 to 10 years than individuals without the syndrome, and have a 5-fold increased risk for T2D [1]. Different components of the MS have been identified as possible stimulus for the synthesis and activity of metalloproteinases (MMPs), like inflammatory and pro-oxidant state, hyperglycemia and dyslipidemia. MMPs constitute a family of more than

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Table 1
Metabolic syndrome definitions according to different Consensus Statements.

National Cholesterol Education Program-Adult Treatment Panel III, 2001 [9]	American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement, 2005 [10]	International Diabetes Federation, 2006 [8]	Harmonizing the Metabolic Syndrome, 2009 [1]
Three or more of the following:	Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Central obesity as defined by ethnic/racial, specific WC and two of the following:	Three or more of the following:
WC>102 cm for men, >88 cm for women	WC>102 cm in men, >88 cm in women	Triglycerides≥150 mg/dl	Central obesity as defined by ethnic/racial, specific WC
Triglycerides≥150 mg/dl	Triglycerides ≥150 mg/dl or on drug treatment for elevated triglycerides	HDL-chol<40 mg/dl for men; <50 mg/dl for women	Triglycerides≥150 mg/dl or on drug treatment for elevated triglycerides
HDL-chol<40 mg/dl in men; <50 mg/dl in women	HDL-chol <40 mg/dL in men; <50 mg/dL in women or on drug treatment for reduced HDL-chol	BP≥130/85 mm Hg	HDL-chol<40 mg/dl in men; <50 mg/dl in women or on drug treatment for reduced HDL-chol
BP≥130/85 mm Hg	BP≥130/85 mm Hg or on antihypertensive drug treatment in a patient with a history of hypertension	FPG≥100 mg/dl	BP≥130/85 mm Hg or antihypertensive drug treatment
FPG≥110 mg/dl	FPG≥100 mg/dl or on drug treatment for elevated glucose		FPG≥100 mg/dl or on drug treatment for elevated glucose

WHR: Waist-to-hip ratio; WC: waist circumference; BP: blood pressure; FPG: fasting plasma glucose; chol: cholesterol.

25 zinc-dependent endopeptidases able to degrade extracellular matrix (ECM) components. MMPs play an important role during physiological tissue remodeling in embryonic development [2], in bone resorption [3], and in angiogenesis [4]. Although synthesized in several tissues and in different physiologic states, their role in vascular pathologies has been extensively studied [5]. However, a loss of activity control may result in diseases such as arthritis, cancer, tissue ulcers, and atherosclerosis among others. Nowadays there is no doubt about the behavior of MMPs in patients with acute myocardial infarction, unstable angina, after coronary angioplasty, suggesting that the importance of MMPs not only in vulnerable plaques but also in restenotic lesions [6]. Circulating levels of some MMPs have been proposed as biomarkers of vulnerable plaques [7]. So, the interest in MMPs has been rapidly increasing during the last years, especially as they could be a relevant target for CVD treatment.

This review summarizes and discusses the effect of the different components of MS, as well as the cluster itself, on MMP behavior.

2. Metabolic syndrome

The coexistence of CVD risk factor components of MS has been known for years, however, in the last two decades, different clinical definition of MS have been developed with the purpose of identifying individuals of high risk. Whatever the uncertainties of definition and etiology, MS represents a useful and simple clinical concept which allows an early detection of T2D and CVD.

For the detection of individuals with MS, six major organizations and societies have arrived at a consensus statement on the definition that will hopefully be a pivotal point in the development of the MS as a tool for clinical and public health use [1]. The consensus definition represents a compromise of sorts between the previous International Diabetes Federation (IDF) [8], the Adult Treatment Panel-III [9] and American Heart Association/National Heart, Lung, and Blood Institute definitions [10] (Table 1).

Prevalence estimated for the MS varies worldwide, in men it ranges from 8% in India to 24% in the United States, while for women it rises from 7% in France to 46% in India [11]. Differences depend in part on lifestyle, sex, age and ethnicity. It is more common in Mexican Americans (32%) and in patients with lower socioeconomic status and sedentary lifestyles, less common in African Americans (22%), and in Europeans (15%) [12]; it increases linearly with age from, about 7% 20–29 year olds to 45% in those over 60. Moreover, the latest NHANES data found that the prevalence of the MS is increasing in both men and women of all age groups [13].

Although the pathogenesis remains unclear, insulin resistance and visceral obesity have been recognized as the most important pathogenic factors. Both of these conditions appear to contribute to the development of MS, although the mechanisms underlying these contributions are not yet fully understood. Atherogenic dyslipidemia, elevated blood pressure and elevated plasma glucose are its most widely recognized components. However, the presences of pro-thrombotic and pro-inflammatory states are also very common. In the insulin resistance state, there is an excessive release of free fatty acids (FFA) and adipocytokines from visceral adipose which are responsible, in part, for the deranged lipoprotein metabolism. The atherogenic dyslipidemia consists not only in the increase of triglycerides and decrease of HDL-cholesterol levels, but also in other alterations that include elevated serum apoprotein B, presence of remnants of triglycerides rich lipoproteins and increased proportion of small dense LDL particles [14]. This modified LDL particle is known to be more atherogenic, probably because of its easy to pass through the endothelial basement membrane, its increased susceptibility to oxidation [15], its higher toxicity to the endothelium and its selective binding to scavenger receptors on monocyte-derived macrophages [16]. Other modified lipoproteins are also frequently found in MS, such as large VLDL over-enriched in triglycerides which could also be more atherogenic [17]. These VLDLs result from a liver with increased lipid deposits [18], characteristic of the MS. The expanded adipose tissue constitutes a source of pro-inflammatory cytokines, thrombotic and atherogenic factors secretion. The C-reactive protein (CRP), a marker of chronic inflammation, is correlated with adiposity, and recent evidence suggests that CRP is not a mere marker of inflammation, but may also directly contribute to atherogenesis and insulin resistance [12].

As was previously emphasized, the number of patients with CVD fulfills the diagnostic criteria of the MS, defined according to any of the most used definitions is increasing daily (Table 1). However, beyond these factors, it is evident that MS constitutes a widespread web involving

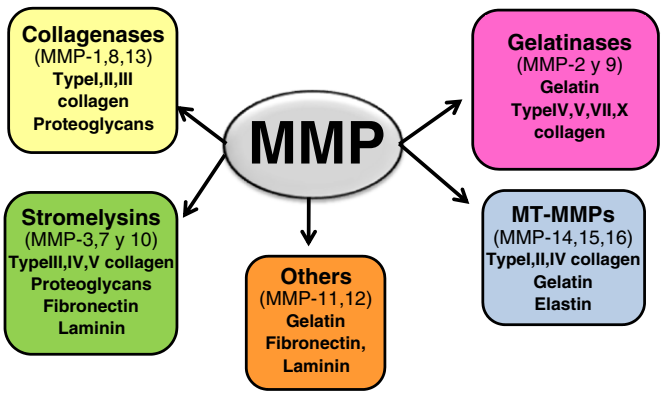

Fig. 1. MMPs classification according to their substrate specificity. In this figure, only extracellular matrix substrates are shown.

Table 2
Behavior of MMP-s in consequence of the different components of the Metabolic Syndrome. The dissimilar results may be explained for the several models used as well as the diversity of methods applied for the measurement of MMPs.

Metabolic syndrome component	MMPs/TIMPs	*In vitro* studies Cell type (Reference)	*In vivo* studies Species (Reference)
Dysglycemia	↑MMP-1	Endothelia cells, macrophages [36]	
	↑MMP-2	Endothelial cells [36]; smooth muscle cells [41]	Rodent aorta [37]; human plasma [47,48]
	↑MMP-9	Endothelial cells, macrophages [36]	Rodent aorta [37]
	↑MT1–MMP	Smooth muscle cells [41]	
	↓MMP-3	Endothelial cells, macrophages [36]	
	↑TIMP-2	Smooth muscle cells [41]	
	↓TIMP-3		rodent aorta [37]
	↑TIMP-1		human plasma [49,50]
Hypertension	↑MMP-2	Arterial tissue [53]	Human plasma [52]
	↑MMP-9	Arterial tissue [53]; smooth muscle cells [57]	Human plasma [52,55,56]
	↑MMP-s		Rodent aorta [54]
	↑MMP-1	Smooth muscle cells [57]	
	↑MMP-3	Smooth muscle cells [57]	
Anti-hypertensive treatment	↓MMP-9	Smooth muscle cells [59]	Human plasma [58]
	↑TIMP	Smooth muscle cells [59]	
Dyslipidemia	↑MMP-9		Human plasma [66]
Hypertriglyceridemia	↑MMP-1		Human plasma [66]
	↑TIMP-1	Macrophages [61]	
Low-HDL	↓MMP-2		Human plasma [65]
	↓MMP-9		Human plasma [7,65]
Oxidized-LDL	↑MMP-1	Vascular endothelial cells [60]	
	↑MMP-9	Macropahges [61]	
	↓TIMP-1	Macrophages [61]	
High-LDL	↑MMP-9		Human plasma [68]
	↑MMP-2		Human plasma [68]
Dense-LDL	↑MMP-2		Human plasma [67]
High-apoprotein B	↑MMP-2		Human plasma [65,67]
Obesity/abdominal obesity	↑MMP-3, 11, 12, 13, 14	Rodent adipose tissue [71]	
	↓MMP-7, 9, 16, 24	Rodent adipose tissue [71]	
	↑MMP-9		Human plasma [75]
	–MMP-9		Human plasma [79]
Decrease weigh	↓MMP-9	Rodent adipose tissue [79]	Human plasma [76]
Inflammation			
CRP-hs	↑MMP-2		Human plasma [66,68], rodents [63]
	↑MMP-9		Human plasma [7,65,68]
	↑MMP-1		Human plasma [66]
Adiponectin	↓MMP-2		Human plasma [68]
	↓MMP-9		Human plasma [68]
	↑TIMP-1	Macrophages [81]	
	↓MMP-9/TIMP-1		Human plasma [82]
	−MMP-1		Human plasma [85]
Leptin	↑MMP-2	Endothelial cells [86]	
	↑MMP-9	Endothelial cells [86]	
TNF-α	↑MMP-2		Rodent [89]
	↑MMP-9		Rodent [89]
	↑TIMP-1		Rodent [89]
IL-1	↑MMP-s	Fibroblasts and smooth muscle cells [91]	
	↓TIMP-2	Fibroblasts and smooth muscle cells [91]	
	↓TIMP-4	Fibroblasts and smooth muscle cells [91]	
NF-Kβ	↑MMP-1, 3, 9	Fibroblasts and smooth muscle cells [91]	

several conditions such as inflammation and pro-coagulant status and hormonal alterations among others.

3. Metalloproteinases

MMPs are able to degrade extracellular matrix (ECM) components such as collagens, proteoglycans, elastin, laminin, fibronectin and other glycoproteins [19]. MMPs comprise a family of 25 identified so far related gene products and, based on sequence homology and substrate specificity, they can be classified into five groups: collagenases, stromelysins, gelatinases, membrane type, and remaining MMPs [4,20] (Fig. 1). Moreover, these enzymes collectively can also cleave several non-ECM proteins, such as adhesion molecules, cytokines, protease inhibitors, and other (pro-) MMPs [21]. MMPs are synthesized by multiple vascular cell types, including endothelial cells, vascular smooth muscles cells, fibroblasts, myofibroblasts, and the systemic-circulatory monocyte and macrophages, as well as the local tissue macrophages.

Most MMPs are secreted as inactive, latent pro-enzymes, and require a proteolytic process to become active. Under normal physiological conditions, the MMP activities are exactly regulated at the transcription level, at precursor zymogens activation, through interaction with specific ECM components, and by inhibition of endogenous inhibitors [22].

The activation of zymogens can be carried out through chemical or proteolitic pathways. In the first case, chemical factors like thiol-modifying agents and oxidized glutathione, reactive oxygens molecules usually produce *in vitro* activation [23]. *In vivo* nitric oxide (NO) has been found to activate pro-MMP-9 during cerebral ischemia, demonstrating a chemical activation of pro-MMP [24]. The proteolitic activation is the most important biologically pathway, and it frequently takes place in an activation cascade by tissue proteinases. On the other hand, MMPs previously activated like MMP-3, MMP-7, and MMP-10 can also activate other secreted pro-MMPs [4]. In fact, MMPs activation requires a

complex cascade of catalytic activation which conduces to an amplified proteolytic effect.

The MMPs with collagenase activities share the ability to cleave fibrillar collagen types I, II, and III into smaller fragments, which in turn can be degraded by other proteases of the MMP family. The most studied collagenases are MMP-1, MMP-8 and MMP-13. Gelatinases consist of MMP-2 and MMP-9, and they are the main enzymes responsible for the degradation of type IV collagen and denatured collagens (gelatins), elastin, fibronectin and laminin, among other proteins.

The tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors of MMPs that participate in controlling the local activities of MMPs in tissues [25]. Four TIMPs (TIMP-1, TIMP-2, TIMP-3 and TIMP-4) have been identified and are able to inhibit the activities of all known MMPs. The four members have many similarities and overlapping specificities, but their biochemical properties and local expression patterns exhibit their distinctive features [26]. Consequently, the net resultant MMP activity in tissues is locally determined by the balance between the levels of activated MMPs and TIMPs.

Related to the focus of this review, the role of MMP in atherosclerosis and in obesity will be briefly described.

3.1. MMPs and atherosclerosis

During the last decade, MMPs have been extensively studied in the pathogenesis of the atherosclerosis process and CVD because of their major significance in vascular remodeling. Different MMPs have been identified in atherosclerotic plaques and in regions of foam cell accumulation and have been directly associated with plaque remodeling as well as plaque vulnerability [27–29]. Gelatinases in general are highly expressed in fatty streaks and atherosclerotic plaques compared to normal regions of the vessel. Fatty streaks and fibroatheromas with hemorrhage and calcification, and fully occluded lesions are enriched in MMP-2 and MMP-9 [30,31]. On the other hand, collagenase MMP-1 expression is undetectable in normal arteries, but has been localized in the fibrous cap and the shoulder regions of carotid atherosclerotic lesions, while macrophages within carotid lesions are the major source of intraplaque MMP-8 formation [32].

Different MMPs acting together could completely degrade the arterial ECM. Extracellular matrix degradation by MMPs could cause reduced fibrous cap thickness and collagen content, which are typical features of vulnerable plaques.

3.2. MMPs and obesity

Expanded fat tissue has demonstrated to be an active organ, where MMPs also exert a role, as has been extensively studied recently.

As it is known, development of obesity is associated with excessive modifications in adipose tissue involving adipogenesis, angiogenesis and proliferation of ECM. Hypertrophy and hyperplasia of adipocytes requires the proliferation and differentiation of preadipocytes. Furthermore, basement basal membrane surrounds adipocytes, therefore it has to be extensively remodeled to allow the hypertrophic development of adipocytes. Observations *in vivo* models suggest that MMPs may contribute to adipose tissue remodeling by degradation of ECM and basement membrane components or by activation of latent growth factors [33]. Moreover, partial inhibition of gelatinolytic activity in mice is associated with moderate effects on adipose tissue development and cellularity [34].

Adipose tissue behavior in relationship to MMP/TIMP balance is also related with the fact that adipocytes are an additional source of circulating MMPs. We should also bear in mind that in obesity, there is an increased secretion of different pro-inflammatory cytokines which, in turn, promote a higher synthesis of MMPs in the vasculature [35]. This issue will be discussed extensively below.

4. Effect of different components of the metabolic syndrome on MMPs

Besides the effect of the proteolitic activation and the TIMPs inhibition, MMPs are also regulated at the transcription level. Different features related with the MS have been identified as possible regulators of MMPs synthesis (Table 2). However, in the study of these enzymes, different factors which can contribute to controversies should be taken into account. Among these factors we can consider, *e.g.*: the cellular diversity in the origin of MMPs, the variety of methods to evaluate MMPs (mRNA synthesis, protein expression, and enzyme activity), and the fact that not all available antibodies distinguish the active forms of these enzymes from their pro-enzyme forms, among other causes. All these factors must be taken into account at the moment of analyzing the results from different studies.

4.1. Hyperglycemia

Several *in vitro* and *in vivo* studies have shown that glucose regulates MMPs. Glucose can modulate the production, expression and activity of MMPs in specific cell lines, however, not all the MMPs respond in the same way. Endothelial cells cultured in hyperglycemic conditions present increased expression and activity of MMP-1, MMP-2 and macrophage-derived MMP-9, but decreased expression and protein levels of MMP-3 [36]. Moreover, in aorta of diabetic rats an increased synthesis of active and latent forms of MMP-2 and MMP-9 was observed [37]. Reactive oxygen species (ROS) are considered a causal link between elevated glucose and metabolic abnormalities [38]. It has been observed that oxidative stress upregulates MMP-9 expression in trophoblast cells from human term placentas [39] and MMP-9 activity in alveolar macrophages from diabetic rabbits [40]. Moreover, ROS and peroxynitrite activate MMP-2 and MT1–MMP in cultured human coronary smooth muscle cells [41]. Recently, under high glucose conditions in retinal endothelial cells, the participation of mitochondrial superoxide scavenger on glucose-induced increased activity of MMP-2, its proenzyme activator-MT1–MMP and the physiological inhibitor-TIMP-2 has been observed [42]. When hyperglycemia impairs activation of the insulin signal pathway resulting in deregulation of eNOS activity, an increased expression and activity of MMP-2 and MMP-9 and reduced TIMP-3 were observed in coronary endothelial cells [43] and in atherosclerotic plaques from subjects with type 2 diabetes [44]. Tarallo et al. studying endothelial cells from umbilical cords in high ambient glucose observed that mRNA expression of MMP-2 and MMP-9 is not affected but their activity increased [45].

In an interesting study design, Sun et al. [46] showed that the effects of hyperglycemia on MMP-2 activity were further enhanced in vascular smooth muscle cells that were exposed to intermittent rather than constant high glucose concentrations, resembling a more pathophysiological model.

There are fewer studies carried out in humans. Derosa et al., evaluated the effect of an oral glucose tolerance test (OGTT) on the level of MMP-2 and MMP-9 in normal and diabetic patients. They observed that both MMPs significantly increased after an OGTT in overweight healthy subjects belonging to the control group and in the diabetic patients. In the former, a peak of MMPs concentration after 2 h was observed, while in the latter the levels continued rising after 3 h, starting from strongly elevated baseline values [47]. In type 1 diabetic (T1D) subjects compared with healthy controls, an increase in MMP-2 plasma activity and it urinary excretion with no concurrent increase in TIMP-1 or TIMP-2 concentrations has been observed [48]. On the contrary, others reported elevated concentrations of MMP-9 and TIMP-1 in plasma of T1D patients [49].

Other controversies have been observed in premature coronary artery disease patients. Nanni et al. observed that blood glucose correlated negatively with MMP-2 activity and positively with TIMP-1

[50], highlighting the importance of evaluating not only MMP activity but also their inhibitors.

Given the controversies observed in human studies, further research is necessary to evaluate the direct impact of glycemia in large vessels, and the behavior of MMPs on apparently healthy subjects, with and without metabolic disorders.

4.2. Hypertension

Blood pressure is one of the major determinants of vessel wall structure and composition. Vascular remodeling is considered an adaptive response to elevation of arterial pressure to normalize the wall tension. This process involves degradation and reorganization of the ECM, as well as hypertrophy and hyperplasia of the vascular smooth muscle cells, contributing to a thickened vessel wall and an augmented vascular stiffness. MMPs play an important role in hypertensive vascular remodeling and dysfunction [51]. They may be involved in the excessive degradation of ECM components, vascular smooth muscle cells migration and proliferation, and intima layer invasion by monocytes.

Increased MMP-2 and MMP-9 levels have been consistently implicated in vascular remodeling associated with hypertension in patients [52] and in animal models [53]. A key characteristic of hypertensive conductance arteries is increased wall thickness accompanied by enhanced rigidity. Nevertheless, using an *ex vivo* model of carotid artery, Flamant et al. have shown that early vascular remodeling in the hypertensive context is actually associated with increased conductance vessel distensibility rather than rigidity. Exposing arteries or vascular cells to stretch induces the release of MMPs. So they hypothesize that increased distensibility may be an early compensatory mechanism allowing vessels to expand in the case of newly elevated pressure [54].

On the other hand, studies in humans show that MMP-9 levels are higher in hypertensive patients than in normotensive controls [55,56]. Most of the related studies also revealed that MMP-9 levels significantly decrease while TIMP-1 levels significantly increase after antihypertensive treatment (*e.g.* Candesartan and Lisinopril), in various body compartment. Moreover, it is known that angiotensin II alone can activate MMPs, given that the expression of MMP-1, MMP-3 and MMP-9 is increased in human vascular smooth muscle cells exposed to angiotensin II [57]. Schieffer et al. studied the effect of angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors on MMP-9 levels in patients with hypertension. In both cases the MMP-9 activity was inhibited. In the case of ARBs, it is suggested that they decrease MMP-9 level directly by their effect of reducing hs-CRP and IL-6, which stimulate MMPs release [58]. On the other hand, the effect of angiotensin-converting enzyme inhibitors could be mediated by an increase in bradykinin level that leads to the release of NO, which in turn experimentally decreases MMP-9 and increases TIMPs levels [59]. NO is a potential regulator of MMP activity in MMP–NO–TIMP complex; however, the contribution of the nitric oxide synthase (NOS) isoforms eNOS and iNOS in the activation of latent MMP is unclear. Gurjar et al. [59] in a smooth muscle cells culture transfected with an eNOS gene observed that high levels of NO was associated with an increase of TIMP-2 levels leading to inhibition of MMP-2 and MMP-9.

4.3. Dyslipidemia

As it is well known, MS dyslipidemia is principally characterized by increased plasma triglycerides, decreased HDL-cholesterol levels and a higher proportion of small dense LDL (the subclass with more atherogenic capacity) [16]. Several studies have investigated the relationship between MMPs and MS dyslipidemia, and strong and interesting associations were found with modified lipoproteins, being oxidation the most frequent modification of lipoproteins. In experimental studies, oxidized LDL has been observed to induce the production of MMP-1 [60] and MMP-9 as well as the decrease in TIMP-1 [61]. Moreover, oxidized LDL favors inflammatory process in the arterial wall, and CRP – the prototypic marker of inflammation – has also been reported to bind to oxidized LDL and promote its uptake by monocyte/macrophage, as an early step of the atheroma development [62]. Recently, Singh U et al. have demonstrated, using an *in vivo* rat model, that administration of CRP promotes both oxidized LDL uptake and MMP-9 production by macrophages [63]. In addition, angiotensin-converting enzyme inhibitors, like imidaprilat, reduce oxidized LDL triggered foam cell formation in macrophages, via modulation of MMP-9 activity through anti-inflammatory mechanisms [64].

Thus, based on the evidences relating LDL oxidation and MMP in the arterial wall, oxidized LDL would also be involved in macrophage-mediated matrix breakdown in the atherosclerotic plaques, thereby predisposing them to vascular remodeling and/or plaque disruption.

In our laboratory, we studied patients with coronary artery disease and observed that plasma activity of MMP-2 and MMP-9 were consistently higher in patients than in controls, and both MMPs activities were significant and positively associated with apoprotein B concentration, while MMP-2 also correlated directly with hs-CRP and correlated inversely with HDL-cholesterol [65]. Other authors have found positive correlations between both MMP-1 and MMP-9 with hs-CRP and triglycerides levels in coronary artery disease patients but not negative ones with HDL-cholesterol levels [66]. In one of the most important prospective studies developed to evaluate the predictor value of MMP-9 of cardiovascular disease in coronary artery disease patients, Blankenberg et al. observed a positive correlation between MMP-9 and hs-CRP, but a weak inverse correlation with HDL-cholesterol [6]. In another of our studies, we evaluated non-diabetic women with and without MS, and observed that women with MS presented higher plasma activity of MMP-2 than controls and that MMP-2 positively correlated with hs-CRP as well as with apoprotein B, dense LDL, triglycerides/HDL-cholesterol index and correlated negatively with HDL-cholesterol. This finding is important since women with MS fit in with an early stage of cardiovascular disease; then, measurement of MMP soluble molecules activity may improve risk assessment, early diagnosis, and probable prognosis of cardiovascular disease [67].

In a study carried out on subjects affected by acquired mixed dyslipidemia, Derosa et al. observed that the serum levels of MMP-2, MMP-9 and their tissue inhibitors were higher than in controls, and correlated with total-cholesterol, LDL-cholesterol and hs-CRP [68].

Given the observed association between lipoproteins – and specifically oxidized LDL – and MMPs, further studies would be necessary to investigate the relationship with other modified lipoproteins, like remnant triglycerides lipoproteins or glycated LDL, which are very common in MS patients and have shown to present high atherogenic properties.

4.4. Obesity/abdominal obesity

Abdominal obesity is one of the main components of MS. As was previously stated, MS is associated with dysfunctional adipose tissue, as a consequence of the enlargement of the adipocytes and the infiltration of macrophages into the tissue that leads to an inflammatory chronic state in the adipose tissue. Expansion of fat cell size would require a pliant extracellular matrix, and recent studies suggested that the absence of such pliant matrix could lead to adipose tissue inflammation, which characterizes the adipose tissue of subjects with insulin resistance [69].

MMPs are involved in two important events of this process, the control of proteolysis and adipogenesis during obesity-mediated fat mass development [70]. To gain further insight into the involvement of the MMPs in the development of adipose tissue, Maquoi et al. monitored the expression of MMPs and TIMPs in adipose tissue from lean and obese mice [71]. This study revealed an upregulation of

mRNA levels of some MMPs (MMP-3, MMP-11, MMP-12, MMP-13, and MMP-14) and downregulation of others (MMP-7, MMP-9, MMP-16, MMP-24 and TIMP-4) in obesity. These modulations differed according to the origin of the adipose tissue (gonadal *vs* subcutaneous), supporting the concept that the different localization of fat deposits present different metabolic behavior [72]. Other studies in obese mice [73] and in obese humans [74] revealed that the main cells that modulate the expression of several MMPs and TIMPs in adipose tissue would be preadipocytes and stromal/vascular compartment cells.

Unal et al. [75] recently studied the expression and activity of MMP-9 in adipose tissue of non-diabetic men, and observed that MMP-9 expression correlated positively with body mass index (BMI) and negatively with insulin sensitivity measured by insulin-modified glucose tolerance test. Moreover, treatment of the patients with pioglitazone resulted in a decrease in MMP-9 expression in adipose tissue through the PPAR-γ mediated inhibition of PKCα. Other evidence supporting the ability of adipose tissue to produce and secrete different MMPs is that weight loss is associated with a pronounced decrease in plasma levels of MMP-9 [76]. These data show that MMP-9 expression in adipose tissue is increased with obesity and insulin resistance.

In an attempt to elucidate the molecular mechanism involved in the production of MMPs, Boden et al. [77] observed in rat aorta that FFA released from the adipocytes and insulin promote the activation of mitogen activated protein kinases (MAPK) activities which are known to stimulate the production of pro-inflammatory cytokines, which in turn promote the activation of MMP-2, MMP-9 and MT1–MMP. Hence, the effects of FFA and insulin on MMPs are likely to be indirect, mediated through cytokines. However, in the liver, hyperinsulinemia has different effects on MMPs, promoting a decrease in the bioactive isoforms of MMP-2, MMP-9 and MT1–MMP [78] suggesting that insulin does not affect MMPs in the same way in different organs. Even though circulating MMPs (especially MMP-9) have emerged as promising biomarkers for human cardiovascular disease, the question is *whether the expanded adipose tissue mass in obesity contributes significantly to the circulating levels of MMP-9*, since the mentioned studies were performed in cell culture or isolated tissues. Recently, Gummersson et al. [79] studied plasma concentration and activity of MMP-9 in men. Although they found that circulating levels of insulin, glucose and hs-CRP as well as blood pressure were related to total and active MMP-9 plasma concentrations, these concentrations were not associated with BMI or with waist circumference. In parallel they also studied the gene expression of MMP-9 in adipose tissue in men with and without MS treated with a weight-reducing diet. There was a lack of association between adipose tissue mRNA and plasma levels of MMP-9, suggesting that this tissue is not a major contributor to circulating MMP-9. Changes in plasma MMP-9 during diet were positively associated with changes in fasting glucose and insulin levels, but not with changes in BMI, waist circumference or adipose tissue MMP-9 mRNA levels [79].

Further studies are necessary to elucidate these controversies and precisely define sites and type of MMPs release in adipose tissue during obesity development.

5. Effects of cytokines and inflammation on MMPs

It is well established that MS is associated with a pro-inflammatory state. This is evidenced by the presence of elevated concentration of inflammatory molecules including CRP and different cytokines, and a decrease in anti-inflammatory molecules. MMPs are also co-expressed or co-repressed in response to inflammatory cytokines and growth factors. MMP promoters are downstream targets within signaling pathways of early response genes; they are induced shortly after cellular stimulation and in the absence of new protein synthesis. These intermediates belong to signaling pathways that are activated by a large variety of ligands, such as IL-1β and TNF-α, and include the nuclear factor kappa B (NF-κB) and the MAPK, among others [80].

5.1. Adiponectin

In reference to adipocytokines, human studies show contradictory results. Adiponectin belongs to the cytokines secreted by adipose tissue and it is inversely associated with obesity and inflammation. Recent data suggest a direct role of adiponectin in atherosclerotic plaque stability through interactions with MMPs and their inhibitors. Adiponectin selectively increased TIMP-1 expression in human monocyte-derived macrophages through the induction of the anti-inflammatory IL-10 [81]. In human studies, Derosa et al. found that adiponectin predicted decreased levels of MMP-2 and MMP-9 plasma levels in patients with combined hyperlipidemia [68]. Moreover, a negative relationship between adiponectin and MMP-9/TIMP-1 ratio has been recently described in patients with acute coronary syndrome; this ratio is considered an independent predictor of the stability of atherosclerotic plaque and the severity of coronary atherosclerosis [82]. These results have been reinforced with the use of VH-IVUS in acute coronary syndrome patients; when investigating the relationship between adiponectin and coronary plaque components, negative correlations between adiponectin levels and percentage of necrotic core were observed [83,84]. However, no correlations have been observed between adiponectin and plasma levels of MMP-1 in coronary patients [85]. As has been mentioned previously, not all types of MMPs might present the same behavior.

5.2. Leptin

Leptin was the first adipose hormone identified; its potential effects on the pathophysiology of cardiovascular complications of obesity remain diverse. Proatherogenic effects of leptin have been described *in vitro*; these effects include, in part, endothelial cells and smooth muscle cell activation, migration, and proliferation [86,87]. Some studies have also shown that leptin plays a role in matrix remodeling by regulating the expression of MMPs and TIMPs. Park et al. [86] 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 cells. This effect would be mediated through the generation of intracellular ROS, and would be decreased by metformin treatment [88]. These findings suggest that leptin, a hormone with pluralistic properties including a mitogenic activity on vascular endothelial cells, plays a role in matrix remodeling by regulating the expression of MMPs and TIMPs. The overexpression of leptin has a role in the growth of atheromatous plaques through its effect on neovascularization and would act as a functional link between adipocytes and the vasculature.

5.3. Other cytokines

In vitro and animal studies have identified the ability of cytokines to regulate the transcription and synthesis of various MMPs. In mice, overexpression of TNF-α leads to increased levels of MMP-2 and MMP-9 and TIMP-1, the latter increase probably as a compensatory effect [89]. Beyond its pro-inflammatory and fibrogenic properties, IL-1 also promotes extracellular matrix remodeling by enhancing cardiac fibroblast MMP expression *in vitro* [90,91] while it downregulates TIMP-2 and TIMP-4 expression levels [91]. NF-κB is required for cytokine upregulation of MMP-1, MMP-3 and MMP-9 in human and rabbit vascular smooth muscle cells and NF-κB inhibition may promote plaque stabilization [92].

However, there are some reports showing that the anti-inflammatory cytokine IL-10 suppressed MMP-2 [89].

Since cytokines augment the production of MMPs with a lower effect on the synthesis of TIMPs, locally secreted cytokines may regulate the regional balance of MMP activity in favor of ECM degradation [92].

Pro and anti-inflammatory cytokines, secreted by adipose tissue or locally in the artery plaque, modulate MMPs and TIMPs synthesis, conditioning the stability of the atherosclerotic plaque.

6. Circulating levels of MMPS in patients with metabolic syndrome

As it is well known and has been previously discussed, patients with MS are twice as likely to develop CVD over the next 5 to 10 years as individuals without the syndrome, and have a 5-fold increased risk for type 2 diabetes mellitus [7]. This cluster of some risk factors and their shared responsiveness to lifestyle modifications suggests that they are not independent one of the other and that they share underlying causes, mechanisms and features [7,10]. Besides considering the recognized components of the MS, the study of further new risk factors associated with this entity will clarify the mechanisms to decrease risk and improve therapeutic conducts. In the last years different researchers have studied the behavior of MMPs in MS and in other associated pathologies. Cicero et al. [93] carried out a study on subjects affected by familial combined hyperlipidemia and/or MS and healthy subjects. They observed that MMP-9, TIMP-1 and TIMP-2 were significantly higher in patients with familial combined hyperlipidemia and MS patients when compared to healthy controls, and in MS patients when compared to patients with familial combined hyperlipidemia. Moreover, TIMP-1 and TIMP-2 were also significantly higher in subjects with MS associated to familial combined hyperlipidemia than in patients with only MS. Gummensson et al. studied circulating levels of MMP-9 in patients with and without MS. They found that patients with MS presented slightly higher circulating MMP-9 levels when using the IDF classification of MS, but not with the WHO or NCEP classification [7]. This last observation may be explained by the fact that only the IDF definition has abdominal obesity as an obligatory criterion for MS, and it has been shown that the macrophage content is much higher in visceral than in subcutaneous fat in men [94].

In our laboratory, we found higher plasma activity of MMP-2 in women with MS [67], which correlates with other soluble molecules involved in the plaque development like sVCAM (data still not published). However, others reported contradictory results, with no differences in MMP-2 activity and higher levels in MMP-9 activity in MS patients (male and female) in comparison to controls [95], or increase in other MMPs, like MMP-8 [95,96]. There is no clear explanation for these controversies. It is possible that gender differences or methodological differences between studies have affected the conclusions; also the fact that our patients were women with MS but without clinical evidence of unstable plaques. The increased MMP-2 activity would be associated with the first steps of the atherogenic process mainly related to the vascular smooth muscle cell migration and intimal thickening. The higher MMP-2 activity might be responsible for a greater matrix degradation of type IV collagen within the basement membrane, and also might activate several growth factors and cytokines, underlying atherosclerotic process in the arterial vessel wall. The lack of MMP-9 detection could be attributed to the fact that this MMP is reported to be associated mainly to the plaque rupture in advanced lesions.

Besides, comparing pre and postmenopausal women with and without MS, Chu et al. [97] observed no differences in MMP-9 among groups, even after the use of estrogen therapy. However, it had been previously reported that oral estrogen therapy in health postmenopausal women produces significant increases in MMP-2 and MMP-9 [98], and others observed decreases in MMP-9 [99]. In view of the controversy, further studies are necessary to understand the behavior of MMPs in reference to changes in female hormones.

Regarding sex hormones, other pathology intimately linked to MS is the polycystic ovarian syndrome (PCOS) which is the most common endocrinopathy of women of reproductive age and exhibits a broad spectrum of metabolic abnormalities, predisposing them to increased cardiovascular risk such as insulin resistance, dyslipidemia, fibrinolytic aberrations, subclinical inflammation, and raised levels of markers of oxidative stress. It has been described that obese women with PCOS have elevated serum concentrations of MMP-2 and MMP-9 [100].

Again, the effect of alteration in sex hormones related to MS should be further investigated in reference to MMP concentration and activity, to understand possible mechanisms associated with cardiovascular risk.

7. Concluding remarks and future perspectives

As we have summarized in this review, several experimental, clinical and epidemiological studies support the effect of MS on synthesis and activity of different MMPs. Over the last years, through the development of animal models of gain or loss-of-function for MMPs, it has been possible to identify of some novel and unexpected functions of MMPs and there has been a substantial increase in the knowledge of the function and characteristics of these enzymes. Nevertheless, further studies in animals and humans are still necessary to elucidate the function of the novel MMPs identified, as well as the role of the already known enzymes in different steps of metabolic diseases.

On the other hand, the presentation of MS as a cluster of risk factors makes the study of each of its components in humans difficult, and the synergistic effect of these risks factors on MMPs synthesis and activity cannot be discarded. Our knowledge of the crosstalk and interactions between them is limited. Multiple factors can modulate atherosclerotic lesions, and little is known about the effects of lifestyle modification on the novel mediators of the atherosclerotic process. Therefore, additional clinical and epidemiological research is needed to unequivocally determine the effect of MS on MMPs synthesized in arterial wall, and their effect on atherosclerosis and vulnerable plaque. Moreover, a rational study of lifestyle modifications as well as pharmacological therapies that would influence MMPs are necessary to generate the information that physicians will probably need to improve the treatment of patients with MS. Understanding the mechanisms of MS impact on MMPs and *vice versa* is an interesting area of research that will positively impact our understanding of the complexity of MS and atherosclerosis.

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