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Evaluation of plasma MMP-8, MMP-9 and TIMP-1 identifies candidate cardiometabolic risk marker in metabolic syndrome: results from double-blinded nested case–control study

*Seyed Mehdi Hoseini, Ali Kalantari, Mohsen Afarideh, Sina Noshad, Aram Behdadnia, Manouchehr Nakhjavani, Alireza Esteghamati**

Endocrinology and Metabolism Research Center (EMRC), Vali-Asr Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Aims. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are dysregulated in metabolic syndrome (MetS) and associated with atherosclerosis and cardiovascular disease (CVD). Previous studies on the association between MMPs/TIMPs and MetS are controversial. We aimed to evaluate circulating MMP-8, MMP-9 and TIMP-1 in a group of MetS individuals and healthy controls to find the potential marker associated with MetS and its components.

Methods. 243 MetS individuals participated in a nested case–control design, of whom 63 were excluded (study subjects for analysis n = 180; 87 MetS cases, 93 controls). We employed the International Diabetes Federation criteria using national waist circumference cutoffs for case definition. Anthropometric and biochemical measurements were done using standard methods.

Results. Plasma MMP-8, TIMP-1, tumor necrosis factor-alpha (TNF-α), highly sensitive C-reactive protein (hs-CRP) and MMP-8/TIMP-1 ratio were significantly higher in MetS cases (P for all < 0.05). Each component of MetS except raised fasting plasma glucose positively correlated with MMP-8 and numbers of MetS components increased with higher MMP-8. In all regression models, MMP-8 was a significant predictor of MetS and in the final model the relationship persisted even after adjusting for pro-inflammatory cytokines hs-CRP and TNF-α (odds ratio = 6.008, 95% confidence interval: 1.612–22.389, P = 0.008).

Abbreviations: MetS, Metabolic syndrome; CVD, Cardiovascular disease; NF-κB, Nuclear factor-kB; IR, Insulin resistance; MMP, Matrix metalloproteinases; TNF-α, Tumor necrosis factor-alpha; ECM, Extracellular matrix; TIMP, Tissue inhibitor of matrix metalloproteinases; IRB, Institutional Review Board; hs-CRP, High sensitivity C-reactive protein; IDF, International Diabetes Federation; WC, Waist circumference; BMI, Body mass index; SYSBP, Systolic blood pressure; DIASBP, Diastolic blood pressure; EDTA, Ethylenediaminetetra-acetic-acid; ELISA, Enzyme-linked immunosorbent assay; FPG, Fasting plasma glucose; CVi, Intra-assay variation; CVe, Inter-assay variation; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; HbA1c, Glycated hemoglobin; HPLC, High-performance liquid chromatography; HOMA-IR, Homeostasis model assessment of insulin resistance; IQR, Interquartile ranges.

* *Corresponding author at:* Endocrinology and Metabolism Research Center (EMRC), Vali-Asr Hospital, Tehran University of Medical Sciences, P.O. Box 13145–784, Tehran, Iran. Tel.: +98 21 88417918; fax: +98 21 64432466.

E-mail addresses: mehdihoseini74@gmail.com (S.M. Hoseini), Ak_eilia@yahoo.com (A. Kalantari), Mhafarideh@gmail.com (M. Afarideh), Sina.noshad@gmail.com (S. Noshad), drarambehdadnia@gmail.com (A. Behdadnia), Nakhjavanim@tums.ac.ir (M. Nakhjavani), esteghamati@tums.ac.ir (A. Esteghamati).

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Conclusion. Strong associations of MMP-8 with components of MetS in univariate, bivariate and multivariate models suggest plasma MMP-8 as a potential cardiometabolic risk marker for MetS. Higher MMP-8 in MetS is possibly mediated through mechanisms both dependent and independent of chronic low grade inflammation.

1. Introduction

Endothelial dysfunction in metabolic syndrome (MetS) patients renders them susceptible for developing cardiovascular disease (CVD) [1,2]. Circulating pro-inflammatory cytokines in their vascular tissues [3] mediate nuclear factor-kB (NF-κB) pathway activation [4] that contributes to a low-grade systemic inflammation associated with atherosclerosis and increased insulin resistance (IR) as important keys to MetS pathophysiology [5]. Proteolytic matrix metalloproteinase (MMP) activity cleaves the extracellular domain of the insulin receptor in a loss of function mechanism that reduces insulin sensitivity [6]. Gradual remodeling of arterial microvasculature in the endothelium and capillary basement membrane is then facilitated by the influx of circulating inflammatory mediators such as C-reactive protein, tumor necrosis factor-alpha (TNF-α) and MMPs to promote inflammatory erosion and thrombosis in MetS atherosclerotic plaques [7]. This has led to suggestions these cytokines may act as CVD predictors [8,9].

MMP-8 is the prototype member of the MMP collagenase family enzymes produced by neutrophils, endothelial cells, smooth muscle cells, and macrophages in atherosclerotic plaques [10]. MMP-8 presents itself at sites of acute inflammation and potently degrades type I collagen, extracellular matrix (ECM) and aids in tissue remodeling of MetS [11]. MMP-8 acts central in the matrix degradation also in chronic inflammatory conditions; association of active enzyme synthesis with unstable angina [10] and correlation between plasma MMP-8 and presence and severity of coronary artery disease [12] underscore the association of MMP-8 levels with the long-term development of adverse systemic CVD [13].

MMP-9 (gelatinase B) is another mediator involved in the vascular remodeling that precedes the atherosclerosis development in MetS. MMP-9 has been best described in older atherosclerotic lesions and is responsible for fibrosis resulting in plaque instability and rupture. This plaque rupture could decide future vascular events in carotid artery atherosclerotic disease [14]; curbing MMP-9 concentrations in MetS has beneficial effects on ECM remodeling and atherosclerotic plaque stability.

MMPs dysregulation is related to atherosclerotic disease changes and to cardiovascular morbidity and mortality. Regulation of MMPs is, however, complex, where transcriptional regulators and tissue inhibitors of MMP (TIMPs) modulate MMP levels and activity, respectively. Published articles concerning MMPs profiles in MetS are scarce and controversial [15–21]. Due to the pro-inflammatory nature of MetS [3] and the fact circulating MMPs levels reflect their activity within atherosclerotic plaques [22], we evaluated plasma concentrations of MMP-8, MMP-9 and TIMP-1 in a group of MetS cases and healthy controls. We selected MMP-8, MMP-9 and TIMP-1 since their alterations are documented with a high cardiometabolic risk in MetS.

2. Materials and Methods

2.1. Study Design, Population and Protocol

Current case–control study is nested within an ongoing Iranian prospective cohort. The primary goal of this program was to reveal the determinants and the outcomes of the cardiometabolic syndrome in a representative population of Tehran (Iranian capital). Systematic subject recruitment for research purposes started in January 2005 with the aid of four health surveillance centers located in the center, east, west, and south of Tehran. We have previously disclosed in-depth details of this cohort program elsewhere [23]. The cohort study group consisted of two subcohorts of diabetic and nondiabetic community dwelling Iranians of Caucasian origin. Subjects with newly diagnosed diabetes in the entry examination comprised the diabetic subcohort. The rest of the participants were included in the nondiabetic subcohort. Subjects with type 1 diabetes, pancreatitis-related diabetes, and malignant conditions (including diabetes in the setting of pancreatic cancer) were not included in the original cohort. Diabetes subjects began their treatment by lifestyle modification, glibenclamide, and/or metformin. Multiple cross-sectional studies demonstrated the characteristics of a selected sample of the original cohort, during years of follow-up [24–29]. Surveyed population for this study was selected from 522 nondiabetic staff of a private company who were under the coverage of eastern health surveillance center (Fig. 1). Details on the sampling and extrapolation of the data to the general population are described elsewhere [24,25]. Invitations were sent to 480 nondiabetic workers of this company from which 243 agreed to participate in this study. Eligibility criteria for the study participants are summarized in Table 1. 63 workers were excluded (due to incomplete data, dilution of case/control differences and presence of exclusion criteria). We analyzed a subsample of 180 participants (87 MetS cases, 93 healthy controls; 111 men and 69 women; 23–70 years) for this study. The prevalence of metabolic syndrome was relatively high in the study population (~30%) and the study was designed to have one control per case. Thus, the study power was estimated to be>99% with a type 1 error of 0.05 and a sample size of 180. All procedures dealing with human subjects where conducted in accordance with the guidelines laid down in the most recent revision of Helsinki declaration. Institutional Review Board (IRB) exemptions for the study protocol were obtained from TUMS ethics committee and each subject provided written informed consent.

Enrolled subjects were interviewed with a pre-designed questionnaire and underwent a detailed history taking and physical examination. Only one of the endocrinologist with substantial expertise in the field (A.E) and blinded to the case/control status examined the participants. A panel of