Letter to the Editor

Extracellular Matrix Turnover: a Balance between MMPs and their Inhibitors

Emre Yalcinkaya[1], Murat Celik[2], Baris Bugan[3]

Aksaz Military Hospital - Departamento de Cardiologia[1], Mugla, Turquia; Gulhane Military Medical Faculty - Departamento de Cardiologia[2], Ankara, Turquia; Malatya Military Hospital - Departamento de Cardiologia[3], Malatya, Turkey

To the Editor,

We read with great interest the article by Santos et al[1], entitled "Early Change of Extracellular Matrix and Diastolic Parameters in Metabolic Syndrome", which was published in october of Arquivos Brasileiros de Cardiologia. The authors[1] aimed to compare diastolic function, biomarkers representing extracellular matrix activity (MMP9 and TIMP1), inflammation and cardiac hemodynamic stress in patients with the metabolic syndrome and healthy controls. We thank authors for their excellent data and valuable study but some comments may be of beneficial.

Matrix metalloproteinases (MMPs) play major roles in tissue development, matrix collagen turnover, repair and remodeling[2-5]. The TIMPs are usually secreted together with variable amounts of their MMPs and regulate MMPs' proteolytic activities by binding tightly to their catalytic sites[2].

Extracellular matrix (ECM) turnover is largely modulated by the interaction between MMPs and their TIMPs.[2-5]A correlation and reciprocal influences between MMP and their TIMP determines the combined effect on ECM turnover[4,5].

Expression patterns of MMP9 andTIMP1 (a specific inhibitor of MMP9), are closely correlated with physiological, pathological and micro-environmental processes characterized by the degradation and accumulation of the ECM[3]. A balance between MMP9 and TIMP1 is a major parameter in regulating both the enzyme activation and functionality in the tissue[3-5]. Consequently, MMP9/TIMP1 ratio could be viewed as a more reliable, useful and determinative marker in the evaluation of their potential prognostic capacities compared with MMP9 and TIMP1 separately. Determining the changes in the ECM balance and activity with a more appropriate method could give a chance to observe the influences on the results more precisely.

Keywords

Matrix Metalloproteinase 1; Matrix metalloproteinase inhibitors; Metabolic X Syndrome; Extracellular matrix.

Mailing Address: EmreYalcinkaya •
Aksaz Military Hospital Department of Cardiology; Aksaz Asker Hastanesi, Kardiyoloji Bolumu, 48750, Aksaz/Marmaris/Mugla, Turkey
Email: dremreyalcinkaya@gmail.com
Manuscript received December 13, 2013; revised manuscript January 7, 2014; accepted January 7, 2014.

DOI: 10.5935/abc.20140061

References

1. Santos AB, Junges M, Silvello D, Macari A, Araújo BS, Seligman BG, et al. Early change of extracellular matrix and diastolic parameters in metabolic syndrome. Arq Bras Cardiol. 2013;101(4):311-6.
2. Roderfeld M, Graf J, Giese B, Salguero-Palacios R, Tschuschner A, Müller-Newen G, et al. Latent MMP-9 is bound to TIMP-1 before secretion. Biol Chem. 2007;388(11):1227-34.
3. Avădanei R, Căruntu ID, Amălinei C, Lozneanu L, Balan R, Grigoraş A, et al. High variability in MMP2/TIMP2 and MMP9/TIMP1 expression in secondary liver tumors. Rom J Morphol Embryol. 2013;54(3):479-85.
4. Cogni AL, Farah E, Minicucci MF, Azevedo PS, Okoshi K, Matsubara BB, et al. Metalloproteinases-2 and -9 predict left ventricular remodeling after myocardial infarction. Arq Bras Cardiol. 2013;100(4):315-21.
5. Kim Y, Remacle AG, Chernov AV, Liu H, Shubayev I, Lai C, et al. The MMP-9/TIMP-1 axis controls the status of differentiation and function of myelin-forming Schwann cells in nerve regeneration. PLoS One. 2012;7(3):e33664.

Reply

We appreciate the thoughtful and valuable comments. It is currently known that the balance between metalloproteinase (MMP) and their tissue inhibitors (TIMP) partly regulates the myocardial extracellular matrix homeostasis. The commenters suggested that the description of the MMP/TIMP ratio would provide additional information about degradation and modulation of collagen synthesis.i,ii. This could be inferred from our previous analysis where patients with Metabolic Syndrome (MS) had higher levels of MMP9 compared to healthy controls, despite similar levels of TIMP1.iii We primarily opted to show these biomarkers individually providing a more comprehensive description of the scenario, considering the individual response and interplay between these biomarkers.

Performing the suggested analysis, the MMP9/TIMP1 ratio was higher in MS compared to controls (2.4 ± 1.1 in MS vs. 1.5± 0.6 in control group, $p < 0.001$), reflecting the original findings. Additionally, in multivariate analysis, higher MMP9/TIMP1 remained associated with MS ($p = 0.006$), independently of the remaining relevant covariates. The higher MMP9/TIMP1 ratio reinforces the concept that an increased turnover of collagen is associated with MS even in this young population. Whether changes in MMP9 individually or in MMP9/TIMP1 ratio have prognostic value in MS remains to be determined.