Kaohsiung Journal of Medical Sciences (2017) 33, 78—85

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Analysis of *MMP-7* and *TIMP-2* gene polymorphisms in coronary artery disease and myocardial infarction: A Turkish case-control study

Ebru Alp [a,*], Akin Yilmaz [b], Murat Tulmac [c], Asiye Ugras Dikmen [d], Atiye Cengel [e], Ridvan Yalcin [e], Emine Sevda Menevse [f]

[a] *Department of Medical Biology, Faculty of Medicine, Giresun University, Giresun, Turkey*
[b] *Department of Medical Biology, Faculty of Medicine, Hitit University, Corum, Turkey*
[c] *Department of Cardiology, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey*
[d] *Department of Public Health, Faculty of Medicine, Gazi University, Besevler, Ankara, Turkey*
[e] *Department of Cardiology, Faculty of Medicine, Gazi University, Besevler, Ankara, Turkey*
[f] *Department of Medical Biology and Genetics, Faculty of Medicine, Gazi University, Ankara, Turkey*

Received 28 July 2016; accepted 13 December 2016
Available online 12 January 2017

KEYWORDS
Coronary artery disease;
MMP-7;
Myocardial infarction;
Polymorphism;
TIMP-2

Abstract Matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP) have a significant role in tissue remodeling related to cardiac function. In earlier studies, *MMP-7* A-181G (rs11568818), C-153T (rs11568819), C-115T (rs17886546), and *TIMP-2* G-418C (rs8179090) polymorphisms have been studied in various diseases. However, association between coronary artery disease (CAD) and these polymorphisms has been poorly studied. The goal of this study is to investigate the association of CAD and myocardial infarction (MI) with *MMP-7* or *TIMP-2* polymorphisms. This study included 122 CAD patients and 132 control individuals. DNA was extracted from whole blood. Polymerase chain reaction-restriction fragment length polymorphism and automated direct sequencing method were used for genotyping of these polymorphisms. No significant differences were found between *MMP-7* A-181G, C-115T, and *TIMP-2* G-418C polymorphism and CAD or MI in a Turkish population. Despite the fact that the genotypes of *MMP-7* C-153T polymorphism had no significant differences among MI and control groups, allele frequencies of C-153T polymorphism were significantly different between the two groups. Our study is the first report to clarify the appreciable relationship

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Medical Biology, Faculty of Medicine, Giresun University, 28200 Giresun, Turkey.
E-mail address: ebrualmaz@hotmail.com (E. Alp).

http://dx.doi.org/10.1016/j.kjms.2016.12.002

between *MMP-7* C-153T polymorphism and MI development in CAD patients. However, these findings also need to be confirmed in other populations so we can improve our knowledge about the genetic factors affecting the development of CAD.

Introduction

Atherosclerosis is the major cause of coronary artery disease (CAD) with stable and unstable periods, and myocardial infarction (MI) can develop in patients throughout the unstable periods in the vascular wall [1]. CAD accounts for more than 80% of sudden cardiac deaths, and the remaining 20% of deaths are caused by other diseases such as cardiomyopathies, left ventricular hypertrophy, and long QT syndrome [2].

According to earlier studies, alteration of the myocardial extracellular matrix (ECM) contributes to the progressive remodeling process [3]. ECM components may cause fragility of the plaque in addition to generation of atherosclerotic and restenotic lesions. Among ECM components, matrix metalloproteinases (MMPs) have a substantial role in initiating acute coronary syndrome [4]. MMPs are a significant family of metal-dependent enzymes and are responsible for ECM degradation [5]. MMP-7 (PUMP-1, matrilysin, E.C.3.4.24.23), an important member of the MMP family, is a protease with wide substrate specificity comprising fibronectin, elastin, type IV collagen, and proteoglycans [6—8]. Whereas active-MMP-7 is 19 kDa, Pro-MMP-7 is 28 kDa [9]. COOH-terminal hemopexin-like domain is not found in MMP-7 [10]. During the acute phase after MI, in particular, it might affect left ventricular remodeling [9]. In addition, it has been proposed that elevation of MMP-7 activity can play a substantial role in CAD [10].

The family of tissue inhibitors of metalloproteinase (TIMP) inhibits the proteolytic activity of MMPs, and it is composed of four members: TIMP-1, TIMP-2, TIMP-3, and TIMP-4 [11]. TIMP-1 potentially blocks the activity of most MMPs including MMP-7, MMP-9, but not MMP-2. However, TIMP-2 is a potent inhibitor of numerous MMPs, excluding MMP-9 as well. TIMP-3 binds MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13, whereas TIMP-4 binds MMP-1, MMP-3, MMP-7, and MMP-9 [4]. Because balance between MMP and TIMP is important, alteration of the ECM compositions can contribute to alteration of myocardial structure or geometry [12]. Altered balance in the MMP—TIMP interaction has been shown to play a significant role in the development of many diseases, including tissue remodeling after cardiac infarction, arthritis, periodontitis, and pulmonary emphysema [13,14]. TIMP-2 expression increases cardiac fibroblast collagen synthesis. Additionally, TIMPs and MMPs pursue a spatiotemporal pattern during myocardium repairing after MI [15]. Earlier, a single nucleotide polymorphism (SNP) in promoter region of *TIMP-2* gene at position 418 has been identified by Hirano et al [16]. This alteration (G-418C, rs8179090), positioned in the consensus sequence of Sp1 binding region, can influence transcriptional activity [12,14,17]. We hypothesized that *TIMP-2* polymorphism might influence CAD, because balance between MMP and TIMP level is important in CAD.

According to a growing body of evidence, MMP gene polymorphisms in their promoters may have brought about variable MMP expressions in distinct individuals [6]. Of the polymorphisms in *MMP* genes, *MMP7* gene polymorphisms are associated with CAD, acute MI, multiple sclerosis, rheumatoid arthritis, and cancers as other MMP genes such as *MMP-9* and *MMP-2* [6,18]. The *MMP-7* gene is localized on chromosome 11q21—q22 and consists of two functional SNP in the promoter region. A-181G (rs11568818) and C-153T (rs11568819) polymorphisms, which are known to modulate the gene expression by affecting the interaction of nuclear binding proteins, have been shown to exert allele-specific effects on the activity of the their own promoters [7,18,19]. Moreover, the combination of −181G allele with −153T allele leads to higher gene expression [20].

The purpose of our study was to compare the distribution of *MMP-7* A-181G (rs11568818), C-153T(rs11568819), C-115T (rs17886546), and *TIMP-2* G-418C (rs8179090) polymorphisms in patients with CAD or MI and control individuals in the Turkish population.

Materials and methods

Study participants

Angiographically characterized 122 CAD patients and 132 controls were included in this study. All CAD patients had ≥50% stenosis in at least one coronary vessel. All samples were obtained from patients and controls admitted to Gazi University (Ankara, Turkey). Existence or absence of an MI history was described by integrating the clinical history data, after a medical records analysis including the typical MI sequelae, enzyme changes, and electrocardiogram on ventricular angiography. While collecting control samples, individuals with a history and clinical or instrumental proof of atherosclerosis in peripheral arteries were excluded from the study group. The controls had undergone coronary angiography following noninvasive cardiac examination because of atypical chest pain. Negligible coronary artery stenosis was left out in this study. All volunteers were from the Turkish population. All patients and controls were interviewed, and records on hypercholestrolemia, hypertension, diabetes mellitus, smoking habits, and family history of CAD were collected. According to the guidelines of the Gazi University of Ethics Committee, informed consent was obtained from all patients and controls. If the blood pressure of patients and controls exceeded 140/90 mmHg or they were given antihypertensive medication, they were described as hypertensive. Meanwhile, diabetes mellitus was diagnosed if the participants had a history of antidiabetic drug treatment, a previous diagnosis, or fasting glucose levels higher than 126 mg/dL. The patients were