Association between paraoxonase-1 gene promoter -108C/T polymorphism and myocardial infarction in the Tunisian male population

Tunuslu erkek populasyonunda miyokard enfarktüs ile paraoksonaz -1 gen başlatıcı -108C/T polymorfizmi arasındaki ilişki

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Abstract: Objective: Human paraoxonase 1 (PON1) is an HDL-associated enzyme with anti-oxidant/anti-inflammatory properties that has been suggested to play an important protective role against coronary artery disease (CAD). The PON1 promoter -108C/T polymorphism has been analyzed in numerous association studies as a genetic marker for CAD, however, with controversial results. The aim of this study was to evaluate the association of PON-1 promoter -108C/T polymorphism with the risk of myocardial infarction (MI) in the Tunisian male population.

Methods: A total of 815 subjects were recruited, including 318 healthy controls and 497 MI patients. Genotypes were determined by PCR-RFLP method. Genotype/allele frequencies were compared in patients and controls using the chi-square test.

Results: Genotype distributions and allele frequencies of PON-1 promoter -108C/T polymorphism were different among the control and MI groups. Patients with MI had significantly higher frequency of the TT genotype compared to controls [29.2% vs. 25.5%; OR (95% CI), 1.67 (1.52–2.49); p=0.010]. The MI patient group showed a significant higher frequency of the T allele compared to the controls [0.56 vs. 0.51; χ²=8.61, p=0.013]. The association between the PON-1 promoter -108C/T polymorphism and MI remained significant after adjustment for other well-established cardiovascular risk factors.

Conclusion: The present study showed a significant and independent association between the PON-1 promoter -108C/T polymorphism and MI in the Tunisian male population.

Keywords: Promoter, gene, polymorphism, myocardial infarction, paraoxonase-1

Özet: Amaç: İnsan paraoksanaz enzimi 1 (PON1), anti oksidan/anti enfiamatuar özelliği olan HDL-ilişkili bir enzim olup koroner arter hastalıklarında (CAD) önemli

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koruyucu rol oynamaktadır. PON1 başlatıcı -108C/T polimorfizmi çeşitli ilişkilendirme çalışmalarda analiz edilmiş CAD için bir genetic marker olarak saptanmış olmakla birlikte ilişkili veriler de bulunmaktadır. Bu çalışmanın amacı PON1 başlatıcı -108C/T polimorfizminin miyokard enfarktüs (ME) riski ile ilişkisini Tunus’lu erkek populasyonunda değerlendirilmesidir.

Metod: Çalışma kapsamında 318 normal ve 497 ME hastası olmak üzere toplam 815 birey incelenmiştir. Genotipler PCR-RFLP metodu ile belirlenmiştir. Kontrol ve hasta genotip/alel frekans karşılaştırırmaları chi-kare testi kullanılarak yapılmıştır.

Bulgular: Kontrol ve MI hasta grupları arasında, PON1 başlatıcı -108C/T polimorfizmi genotip dağılımları ve alel frekansları farklı olarak bulundu. ME hastalarında TT genotipi kontrolle göre anlamlı olarak yüksek idi [29.2% vs. 25.5%; OR (95% CI), 1.67 (1.52–2.49); p=0.010]. Ayrıca, ME hasta grubunda T aleli frekansı kontrol grubuna göre anlamlı olarak yüksek bulundu [0.56 vs. 0.51; χ²=8.61, p=0.013]. PON1 başlatıcı -108C/T polimorfizmi ve MI arasındaki ilişki diğer iyi tanımlanmış kardiyovasküler hastalık faktörlerine göre düzeltmeler yapıldığında da anlamlı olarak yüksek bulundu.

Sonuç: Bu çalışma Tunuslu erkek populasyonunda, PON1 başlatıcı -108C/T polimorfizmi ve ME arasında anlamlı ve bağımsız ilişki olduğunu göstermektedir.

Anahtar Kelimeler: Başlatıcı, gen, polimorfizm, miyokard enfarktüsü paraoksonaz-1

Introduction

Coronary artery disease (CAD) is a common complex and multifactorial disorder and has become a major source of morbidity and a leading cause of death in different parts of the world [1,2]. Apart from the environmental risk factor for CAD it has been associated with multiple genetic factors, including mutations and polymorphisms to several genes, with risk of cardiovascular disease [3,4]. The gene encoding human paraoxonase 1 (PON1) has been implicated in conferring genetic susceptibility to CAD [5,6]. The PON1 gene is located on the long arm of chromosome 7 between q21.3 and q22.1 with other members of its supergene family [7,8]. Several polymorphisms have been identified in the PON1 gene. Two of them are located in the coding region, a leucine to methionine substitution at position 55 (L55M, rs854560) and a glutamine to arginine substitution at position 192 (Q192R, rs662). The role of these polymorphisms in predicting atherosclerosis remains controversial, several studies revealed a significant association between PON1 coding region polymorphisms and CAD risk [9–11] while others reported a lack of association [12–14]. We have previously confirmed an association between the Q192R and MI in Tunisian male subjects [15]. Another important polymorphism is located in the promoter region, the -108C/T (rs705381) polymorphism (sometimes denoted as -107; see Furlong et al. [16], for comments on nomenclature). It has been shown to have a dominant effect on PON1 gene expression and enzymatic activity [17]. This polymorphism was reported to be associated with low arylesterase activity and CAD by several investigators [18,19] but not by others [20]. Considering the contradictory results, we proposed to evaluate the impact of the -108C/T variant of the PON1 gene on MI risk in a sample of the Tunisian male population.

Materials and Methods

Study population

A total of 815 unrelated individuals were included in the study. Four hundred and ninety seven male patients with MI were enrolled from the Department of Cardiology, Rabta University Hospital of Tunis, from February 2009 to August 2012. The mean age of this group was 54 years (SD 9). Diagnosis of MI was confirmed according to the European Society of Cardiology criteria; a typical rise and fall of CK-MB, with at least one of the following criteria: ischemic symptoms, development of pathologic Q waves on the ECG, ECG changes indicative of ischemia (ST segment elevation or depression). We excluded patients with septicaemia, liver cirrhosis, renal failure, colitis, cardiomyopathy, congenital heart disease, rheumatic heart disease, neurological and cancer problems. The control group included 318 male subjects’ volunteers, with no history of angina pectoris or MI, and with a normal electrocardiogram. Their mean age was 54 years (SD 8). Controls with familial history CAD and taking medications determined by interviewing, were excluded from the study. Patients and controls were homogeneous Tunisian Arab descendants who resided in Tunisia and all were from North Tunisia. Informed written consent was obtained from all participants and the design of the study was approved.
by the local ethics committee. Weight and height were measured on the subjects barefooted and lightly clothed. Body mass index (BMI; kg/m²) was calculated and obesity was defined as BMI ≥30 kg/m² [21]. Diabetes mellitus was defined as hyperglycemia, requiring antidiabetic drugs or testing blood glucose over 7.0 mmol/L. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or the use of antihypertensive drug treatment. Dyslipidemia was defined as a total cholesterol (TC) level >6.47 mmol/L and/or triglyceride (TG) level >2.26 mmol/L. A smoker was defined as a current smoker or an ex-smoker.

**Laboratory analysis**

Biochemical measurements were determined from blood sample collected by venipuncture after overnight (>12 h) fast. Plasma levels of TC, TG and HDL-cholesterol (HDL-C) were measured by standardized enzymatic methods using commercial kits (Roche Diagnostics, Mannheim, Germany) on a Hitachi 912 analyzer. LDL-cholesterol (LDL-C) was calculated using the Friedewald equation when the triglyceride concentrations did not exceed 4.8 mmol/L [22].

**DNA analysis**

Genomic DNA was extracted from peripheral blood leukocytes by phenol-chloroform method. The -108C/T polymorphism (rs705381) of the PON1 gene was identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with few modifications as described previously [23]. Briefly, PCR was carried out using the forward primer 5’-AGCTAGCTGCCGACCGGGAGGAG-3’ and the reverse primer 5’-GGCTGCAGCCCTCACCCACAACCC-3’ resulting in an amplified fragment of 240 bp in size. The PCR reaction mixture contained 100 ng DNA template, 0.5 µM of each primer, 1.5 mM MgCl₂, 200 µM 4dNTP’s and 1 U Taq DNA polymerase (MBI Fermentas). After denaturing the DNA for 5 min at 94°C, the reaction mixture was subjected to 35 cycles of 1 min at 94°C, 1 min at 60°C and 1 min at 72°C with a final extension time of 7 min at 72°C.

The 240 bp PCR product was digested with 5 U BsrBI restriction endonuclease (MBI Fermentas, Lithuania) overnight at 37°C and the digested products were separated on a 3% agarose gel electrophoresis, visualized by ethidium bromide staining under an ultraviolet illuminator. Digestion of PCR product by BsrBI yields 240 bp fragment for the TT genotype, 212 bp and 28 bp fragments for CC genotype and 240 bp, 212 bp and 28 bp for the CT genotype (Figure 1). To ensure that the genotyping was adequate quality, all gels were reread blindly by 2 persons without any change, and 20% of the analyses was repeated randomly.

**Statistical analysis**

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 10.0 for Windows; SPSS Inc., Chicago, IL, USA). Allelic frequencies were calculated by gene-counting method. Differences between the means of the 2 continuous variables were evaluated by Student t-test. Differences between non continuous variables, genotype distribution, and Hardy-Weinberg equilibrium were tested by χ² analysis. Data for triglyceride were log transformed to reduce skewness of the data.

Odds ratio (OR) together with their 95% approximate confidence intervals (95% CI) were calculated as estimators of the relative risk of MI for the -108C/T PON1 genotypes. A binary logistic regression analysis was performed for the determination of the independent predictors for MI. A two-tailed p-value <0.05 was considered statistically significant.

**Results**

The demographic and clinical characteristics of the study population are shown in Table 1. There were significant differences for age (p=0.003), BMI (p=0.022), and the frequencies of diabetes (p<0.001), hypertension (p<0.001),
obesity (p<0.001) and smokers (p<0.001) between the MI patients and control group.

The baseline serum concentrations of TG and LDL-C were higher in MI patients than controls (p<0.001). In addition, MI patients presented lower HDL-C levels (p<0.001).

The genotype distribution and the relative allele frequency of the -108C/T polymorphism at the PON1 gene in MI patients and control subjects are shown in Table 2. Genotype frequencies were in agreement with those predicted by the Hardy-Weinberg equilibrium in control subjects (χ²=5.21; p=0.074) and MI patients (χ²=3.36; p=0.186). The MI patient group showed a significant higher frequency of the T allele compared to the controls (0.56 vs. 0.51; χ²=6.46, p=0.01). The OR for MI risk among carriers of T allele was 1.28 (95% CI: 1.05–1.58; p=0.01). In comparison to the CC homozygotes, the OR (95% CI) for MI was 1.62 (1.13–2.30) for CT heterozygotes and 1.67 (1.52–2.49) for TT homozygotes (Table 2).

We used binary logistic regression to test for independent correlates of the presence of MI risk. Included in the model were age, smoking, diabetes mellitus, dyslipidemia, smokers and the -108C/T polymorphism. Age (p<0.001) diabetes mellitus (p=0.034), obesity (p<0.001), dyslipidemia (p=0.009) and the -108C/T polymorphism were independent correlates of the presence of MI risk (Table 3). When clinical and laboratory values were compared among genotype in the patient group, no significant differences were noted with regard to body mass index, TC, TG, HDL-C and LDL-C levels (Table 4).

**Table 2:** Distribution of genotypes and unadjusted odds ratio and 95% confidence intervals of the presence of myocardial infarction (MI) among -108C/T genotypes.

| Genotypes | MI patients (n=497) | Controls (n=318) | Unadjusted odd ratios | P |
|-----------|---------------------|-------------------|-----------------------|---|
| Genotypes |                     |                   |                       |   |
| CC        | 94 (18.9%)          | 88 (27.7%)        | 1                     |   |
| CT        | 258 (51.9%)         | 149 (46.9%)       | 1.62 [1.13–2.30]      | 0.007 |
| TT        | 145 (29.2%)         | 81 (25.5%)        | 1.67 [1.52–2.49]      | 0.001 |
| Alleles   |                     |                   |                       |   |
| C         | 0.44                | 0.49              |                       |   |
| T         | 0.56                | 0.51              | 1.28 [1.05–1.58]      | 0.01 |

**Discussion**

CAD is a multifactorial disease in which genetic and environmental factors play a great role. These factors may differ in each race or ethnic group. In the current report, we have undertaken a case–control study to investigate the role of the -108C/T polymorphism in the promoter of PON1 gene in susceptibility to MI in Tunisians population. Both patients with MI and controls belonged to the same ethnic background and all shared a common geographic origin in North Tunisia.

To our knowledge, this is the first study reporting the frequency of -108C/T Polymorphism of PON1 gene in susceptibility to MI in Tunisians. We demonstrated that...
the -108C/T polymorphism in the promoter of PON1 gene was associated with MI in Tunisian male patients. We found an excess of homozygosity of the -108TT variant among MI patients compared with control subjects as was the frequency of the T allele. Multivariate analysis showed that this association was independent of other traditional risk factors of CAD. The -108C/T polymorphism has been studied in different populations, with the CT genotype being the most common in most studies. The T allele frequency of -108C/T polymorphism in controls varied considerably among populations and range from 0.38 in Caucasians to 0.85 in African-Americans [24–26], whereas it is 0.51 in our population, which are among the reported values, although closer to Caucasian populations [24]. Previous clinical studies that have investigated the relationship between PON1 -108C/T polymorphism and CAD are not many, and have produced inconsistent results, probably because of variations due to the different ethnic origins of study groups and some intervening factors [27–29]. Najafi et al. reported an association between -108C/T polymorphism and CAD in Iranian patients [30]. Similarly, James et al. found the T allele to be a risk marker for CAD in a Swiss population of diabetics [31]. In contrast, to the results of the present and the aforementioned studies, Wang et al. did not find any association of the -108C/T polymorphism with CAD in a large study on Chinese men [32]. A large meta-analysis by Wheeler et al. of 43 genetic association studies involving more than 11,000 cases and 13,000 controls found no significant link of the -108C/T polymorphism with CAD [9]. Inoue et al. found no significant difference in the -108 allele distribution between normal individuals and those with type 2 diabetes mellitus [33]. Two studies on European populations with hypercholesterolemia could not find any association between -108C/T variant and carotid intima–media thickness [34,35]. Gupta et al. have recently reported that -108C/T polymorphism was not associated with CAD risk after adjusting for conventional risk factors in North-West Indian Punjabis [36]. On the other hand, Leviev et al. observed that -108CC genotype protected against the risk of CAD in patients aged 60 or younger (OR: 0.60; 95% CI: 0.37–0.90) but not in older patients [37]. Also, Ahmad et al. reported in Asians Indians, a protective trend against CAD in a case-control study involving 204 patients with CAD and 178 healthy control subjects [38].

The reason for this discrepancy remains unclear. These different results are likely to be a consequence not only of the different sample sizes or the different allelic frequencies observed in different ethnic groups, but also and most importantly of different selection criteria adopted for patients and controls, in particular clinical presentation, extent of disease, age, race, geographical area, concomitant environmental risk factors like differences in the lifestyles (smoking, diet, and exercise) and the interactions, gene-gene and gene environment or different linkages to the polymorphism determining MI risk. Another explanation could be that a putative disease-marker could be population specific or that the non-random associations between the marker alleles and the important mutations may differ among populations.

There were limitations in the present study: (1) all patients enrolled in this study were men. (2) In addition, given that the controls were younger than the cases, it is possible that some of controls become cases when they get old as the cases. (3) Coronary angiography was not performed in controls subjects, who were without symptoms and without history of any form of vascular events. (4) We did not measure paraoxonase concentration and enzyme activity, thus the influence of PON1 genetic polymorphisms on PON1 concentration has not been investigated. (5) Further studies on the linkage of the -108C/T polymorphism with other loci of the PON1 gene in Tunisian are required, as they may be able to confirm the findings we obtained.

In conclusion, the present study showed a significant and independent association between the -108C/T

| Table 4: Demographic and clinical characteristics across -108C/T PON1 genotype of MI and control groups. |
| --- |
| **Patients (n=497)** | **Controls (n=318)** |
| **CC (n=94)** | **CT (n=258)** | **TT (n=145)** | **p** | **CC (n=88)** | **CT (n=149)** | **TT (n=81)** | **p** |
| Age (years) | 52.8±9.09 | 54.7±8.84 | 54.2±9.11 | 0.30 | 52.0±8.38 | 52.0±8.62 | 52.8±9.38 | 0.79 |
| BMI (kg/m²) | 25.9±3.80 | 25.3±3.63 | 25.4±3.55 | 0.65 | 26.2±4.90 | 26.2±4.86 | 26.4±5.24 | 0.94 |
| Total cholesterol (mmol/l) | 4.8±0.52 | 4.89±0.45 | 4.92±0.40 | 0.87 | 4.94±0.39 | 4.76±0.37 | 4.86±0.28 | 0.32 |
| Triglycerides (mmol/l) | 1.8±0.75 | 1.81±0.72 | 1.9±0.80 | 0.60 | 1.4±0.79 | 1.5±0.90 | 1.4±0.59 | 0.55 |
| HDL-cholesterol (mmol/l) | 0.3±0.11 | 0.33±0.09 | 0.32±0.09 | 0.27 | 0.4±0.11 | 0.45±0.12 | 0.43±0.10 | 0.48 |
| LDL-cholesterol (mmol/l) | 1.2±0.47 | 1.27±0.40 | 1.26±0.35 | 0.90 | 1.1±0.36 | 1.10±0.35 | 1.18±0.25 | 0.12 |

BMI: Body mass index.
polymorphism in the promoter region of the PON1 gene and MI in the Tunisian male population. Further studies are necessary for confirming the relationship between MI and this variant and clarifying the molecular mechanism underlying this association.

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Conflict of Interest: The authors have no conflict of interest.

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