VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2012, Vol. 19, No. 4, pp. 381–386
10.5603/CJ.2012.0069

ISSN 1897–5593

Oxidative stress and severity of coronary artery disease in young smokers with acute myocardial infarction

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Abstract

Background: *Cigarette smoking increases the oxidative stress mediated vascular dysfunction in young adults. We aimed to investigate the relation between the oxidative stress indices and coronary artery disease (CAD) severity in young patients presenting with acute myocardial infarction (AMI).*

Methods: *Young patients (aged < 35 years) who were admitted consecutively to our hospital with a diagnosis of AMI were included in the study. Age matched healthy subjects were selected as controls. Oxidative stress indices including lipid hydroperoxide (LOOH), total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), paraoxonase (PON) and arylesterase (ARE) activities were measured in serum. CAD severity was assessed by calculating the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery Study) score. We analyzed the association between the oxidative indices and CAD severity.*

Results: *Forty two young patients were admitted to the hospital with AMI (age 32.4 ± 2.6 years; 39 males, 3 females). Current and heavy smoking was commonly observed among the patients (79%). All patients underwent emergency coronary angiography. Twenty-eight healthy subjects were selected as controls. Patients had significantly higher OSI and TOS levels (median, interquartile range) [0.44 (0.26–1.75)* vs *0.25 (0.22–0.30), p < 0.001 and 6.0 (4.4––20.8)* vs *4.1 (3.7–4.6), p < 0.001], respectively, and lower TAS and LOOH levels [1.6 ± 0.1* vs *1.7 ± 0.1, p = 0.02 and 3.0 ± 0.8* vs *3.6 ± 0.4, p= 0.001], respectively, compared to the control group. CAD severity correlated positively with OSI (r = 0.508, p = 0.001) and TOS levels (r = 0.471, p = 0.002). Subjects with an intermediate to high SYNTAX score (≥ 22) demonstrated significantly higher OSI (median, interquartile range) [0.40 (0.34–1.75)* vs *0.34 (0.26–0.68), p = 0.01] and TOS [6.9 (4.4–20.8)* vs *5.8 (4.5–11.4), p = 0.01] levels compared to subjects with low SYNTAX score.*

Conclusions: *Oxidative stress is an important contributor to CAD severity among young smokers. Elevated OSI and TOS levels reflect disease severity and vascular damage related to heavy smoking in early onset CAD.* (Cardiol J 2012; 19, 4: 381–386)

Key words: young smokers, myocardial infarction, oxidative stress, OSI, TOS

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Received: 29.02.2012 Accepted: 09.04.2012

Introduction

Morbidity and mortality from coronary artery disease (CAD) remain high in Turkey [1]. The EUROASPIRE III study showed that 20% of the subjects who are hospitalized with CAD in Turkey are below 50 years of age. In fact, Turkey has the highest prevalence of premature CAD of all the populations [2]. The underlying reasons may relate to ethnic differences in CAD risk factor distribution across different populations. For instance, low levels of high-density lipoprotein cholesterol (HDLC) and high prevalence of cigarette smoking are more common in Turkey than in other populations [1, 2]. Premature onset CAD can occur even in the absence of traditional risk factors (hypertension, hyperlipidemia and diabetes mellitus) [3]. Hyperlipidemia and smoking can initiate oxidative stress and atherosclerosis in young subjects [4]. Cigarette smoking is highly prevalent in Turkey. Cigarette smoking increases oxidative stress mediated vascular dysfunction in young adults [5]. Increased oxidative stress is a critical factor particularly in young cigarette smokers with low levels of anti-oxidant effects of HDLC, as observed in Turkey [1, 2]. In this study, we investigate oxidative stress indices and CAD severity among young patients who presented to hospital with acute myocardial infarction (AMI).

Methods

This study was conducted between 2009 and 2011. Consecutively admitted young patients (aged < 35 years) with AMI, and who underwent coronary angiography, were included in the study. Patients who had normal coronary arteries were excluded. Subjects with a prior history of cardiovascular or renal disease, malignancy, significant comorbidities, and who were taking medication (i.e. statins) that could influence oxidative status, were excluded from the study. Current cigarette smokers were asked about the extent and duration of their smoking. Heavy cigarette smoker status was defined as consuming ≥ 20 cigarettes (1 pack) per day (1 pack-year = 1 pack per day for a year) [6]. Informed consent was obtained from all participants prior to their enrollment in the study. The study was approved by the Institutional Review Board.

Blood samples

Blood samples were withdrawn into heparinized tubes, with the initial blood draw at the earliest possible time after hospital admission and before start of medication. Serum was separated by centrifugation at 3000 rpm, for 10 min and stored at –80°C until analysis for the oxidative indices.

Serum biochemistry

Biochemical analyses were conducted at an accredited laboratory. The total antioxidant status (TAS) and total oxidant status (TOS) levels of serum were measured as described previously [7, 8]. The oxidative stress index (OSI) was calculated as the ratio of TOS to TAS. Plasma lipid hydroperoxide levels (LOOH) were measured by the automated ferrous ion oxidation xylenol orange (FOX-1) assay method. Paraoxonase (PON) and arylesterase (ARE) activities were measured spectrophotometrically (Rel AssayR, Turkey).

The unit for total antioxidative capacity of plasma (TAS), is expressed as mmol Trolox equivalent/L, and the total oxidant status of plasma (TOS) as the micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L). OSI is calculated as the percentage ratio of the total peroxide to the TAS level [9].

The SYNTAX score

The severity of CAD was assessed by a Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery Study (SYNTAX) score. Briefly, SYNTAX characterizes the degree of coronary disease complexity based on anatomical observations [10]. The scores were calculated based on angiographic findings by independent operators [10].

Statistical analysis

Statistical analysis was performed using the Statistical Program for Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as a median (interquartile range) for numerical variables that did not display normal distribution, and in percentages for categorical variables. A comparison of means between study groups was performed by an independent sample t-test for variables with normal distribution. The Mann-Whitney U test was used for variables with a non-normal distribution (OSI, TOS and median cigarette consumption). Multivariate analysis was performed by linear regression to find the predictors of severity of CAD. The covariates were the oxidative stress indices (LOOH, TAS, TOS, OSI, PON and ARE). The level of significance was set at $p < 0.05$.

Results

Forty-two young patients (< 35 years of age) were admitted consecutively to our hospital with

a diagnosis of AMI (mean age 32.4 ± 2.6 years; 39 [93%] males). Seventeen (40.4%) patients had ST elevated MI, and 25 (59.5%) patients had non ST elevated MI. All patients were newly diagnosed with CAD. Smoking was the most prevalent CAD risk factor; 33 (79%) patients reported that they had been smoking heavily. Median (interquartile range) cigarette consumption was 12 (8–22.5) pack-years. All smoker subjects were heavy smokers based on the definition provided [6]. The control group had 12 (42.8%) subjects with a smoking history, and all of these were heavy smokers [6]. The median (interquartile range) consumption of the control group was 11 (8–18) pack-years. The number of heavy smokers was higher among the patients, as compared with the control group ($p = 0.02$). None of the patients were taking any medication at the time of admission.

CAD severity

All patients underwent coronary angiography. Severe CAD (≥ 70% narrowing in at least one major coronary artery > 2 mm) was observed in all subjects. Twenty five (59.5%) patients underwent percutaneous coronary intervention (PCI), 5 (11.9%) patients received coronary artery bypass surgery, and medical treatment alone was given to 12 (28.5%) subjects. In the medical treatment group, 7 (16.6%) patients had noncritical coronary lesions likely after spontaneous clot lysis and recanalization of the culprit lesion. Five (11.9%) patients had critical coronary artery lesions that were not amenable to either PCI or surgery. Patient characteristics are displayed in Table 1. The SYNTAX score was calculated for all subjects. Thirty (71.4%) subjects displayed a low SYNTAX score (< 22) and 12 (28.5%) subjects had moderate to high SYNTAX scores (≥ 22) [11].

Oxidative indices

Oxidative indices are listed in Table 2. Twenty eight subjects without CAD risk criteria and with no prior history of vascular disease were selected as controls. OSI and TOS levels were significantly higher in the CAD subjects compared to the controls. The control group median (interquartile range) TOS levels were 4.1 (3.7–4.6) compared to 6.0 (4.4–20.8) in the patient group ($p < 0.001$). The control group median (interquartile range) OSI levels were 0.25 (0.22–0.30) compared with 0.4 (0.26––1.75) in the patient group ($p < 0.001$) (Table 3). On the other hand, TAS and LOOH levels were higher in the controls compared to the CAD group (1.6 ± 0.1 *vs* 1.7 ± 0.1, $p = 0.02$ and 3.0 ± 0.8 *vs* 3.6 ± 0.4, $p = 0.001$, respectively). OSI levels correlated positively with TOS and negatively with TAS (TOS/TAS).

Table 1. Characteristics of premature coronary artery disease patients (n = 42).

Age (years)	32.4 ± 2.6
Male gender	39 (93%)
Heavy smokers	33 (79%)
Median cigarette consumption [pack-year]	12 (8–22.5)
Diabetes mellitus	2 (5%)
Family history of CAD	16 (38%)
Weight [kg]	81 ± 13
Height [cm]	1.72 ± 0.06
BMI [kg/m^2]	27.3 ± 4.5
Fasting blood glucose [mg/dL]	103 ± 27
Urea [mg/dL]	15 ± 7
Creatinine [mg/dL]	1.1 ± 0.9
Total cholesterol [mg/dL]	189 ± 55
Triglycerides [mg/dL]	164 ± 89
LDL cholesterol [mg/dL]	120 ± 50
HDL cholesterol [mg/dL]	37 ± 9
SYNTAX score	12.6 ± 9.4

CAD — coronary artery disease; BMI — body mass index; LDL — low-density lipoprotein; HDL — high-density lipoprotein

Table 2. Oxidative indices among patients with low *vs* high SYNTAX scores.

	Low SYNTAX (n = 30)	High SYNTAX (n = 12)	P
PON activity [U/L]	142.4 ± 119.1	160.0 ± 146.04	0.688
ARE activity [U/L]	506.4 ± 140.4	564.9 ± 123.1	0.195
TOS [μmol H_2O_2 Eq/L]	5.8 (4.5–11.4)	6.9 (4.4–20.8)	**0.01***
TAS [μmol trolox Eq/L]	1.65 ± 0.26	1.70 ± 0.33	0.584
OSI [arbitrary unit]	0.34 (0.26–0.68)	0.40 (0.34–1.75)	**0.01***
LOOH [μmol H_2O_2]	2.8 ± 0.9	3.3 ± 0.9	0.100

*Comparison between patient and control groups by Mann-Whitney U test; PON — paraoxonase; ARE — arylesterase; TOS — total oxidant status; TAS — total antioxidant capacity of plasma; OSI — oxidative stress index; LOOH — lipid hydroperoxides

Table 3. A comparison of clinical characteristics and serum oxidative indices in patients and in controls.

	Patients (n = 42)	Control group (n = 28)	P
Age [years]	32.4 ± 2.6	31.7 ± 2.1	0.2
Male gender	39 (93%)	23 (82%)	0.2
BMI [kg/m^2]	27.3 ± 4.5	26.5 ± 4.8	0.5
Heavy smokers	33 (79%)	13 (46.4%)	0.02
Median cigarette consumption [pack-years]	12 (8–22.5)	11 (8–18)	0.2*
Hypertension	0	0	–
Total cholesterol [mg/dL]	189 ± 55	196 ± 52	0.6
Triglycerides [mg/dL]	164 ± 89	143 ± 35	0.2
LDL [mg/dL]	120 ± 50	121 ± 44	0.9
HDL [mg/dL]	37 ± 9	40 ± 8	0.1
PON activity [U/L]	131.9 ± 81.1	140.2 ± 19.4	0.6
OSI [arbitrary unit]	0.4 (0.26–1.75)	0.25 (0.22–0.30)	**< 0.001***
TOS [μmol H_2O_2 Eq/L]	6.0 (4.4–20.8)	4.1 (3.7–4.6)	**< 0.001***
TAS [μmol trolox Eq/L]	1.6 ± 0.1	1.7 ± 0.1	**0.02**
ARE activity [U/L]	531.0 ± 118	515.8 ± 86	0.5
LOOH [μmol H_2O_2]	3.0 ± 0.8	3.6 ± 0.4	**0.001**

*Comparison between patient and control groups by Mann Whitney U test; BMI — body mass index; LDL — low-density lipoprotein; HDL — high--density lipoprotein; PON — paraoxonase; ARE — arylesterase; TOS — total oxidant status; TAS — total antioxidant capacity of plasma; OSI — oxidative stress index; LOOH — lipid hydroperoxides

Oxidative indices and CAD severity

CAD severity (SYNTAX score) showed significant and positive correlation with both OSI ($r = 0.508$, $p < 0.001$) and TOS levels ($r = 0.471$, $p < 0.001$).

Subjects with an intermediate to high SYNTAX score (≥ 22) demonstrated significantly higher OSI (0.40 [0.34–1.75] *vs* 0.34 [0.26–0.68], $p = 0.01$) and TOS (6.9 [4.4–20.8] *vs* 5.8 [4.5–11.4], $p = 0.01$) levels, compared to the low SYNTAX score group (Fig. 1).

Finally, linear regression analysis was performed to find the predictors for CAD severity score among patients with early onset CAD. Among covariates of the 6 oxidative indices, OSI was the only oxidative stress parameter predictive of CAD severity (SYNTAX score) ($r = 0.508$, $p < 0.001$).

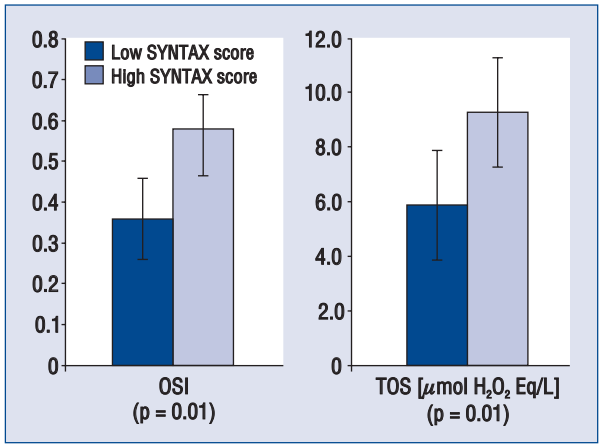

Figure 1. Oxidative stress index (OSI), total oxidant status (TOS), subjects with low (< 20) and intermediate to high (≥ 22) SYNTAX scores.

Discussion

We investigated CAD severity in relation to oxidative stress indices in young patients after MI. The study population had a very high prevalence of heavy smoking (79%) reflecting the crucial role of smoking in early onset CAD. Furthermore, CAD severity showed significant and positive correlation with oxidative stress indices. CAD patients had significantly higher OSI and TOS, and lower TAS and LOOH than the healthy controls. Our observations indicate that oxidative stress is important role in the pathogenesis of early onset CAD, particularly among young smokers.

The distribution of oxidative indices among young subjects with early onset CAD remains to be elucidated. Our study is the first study to evaluate the role of oxidative stress among young patients with severe CAD.

Previous studies have demonstrated that oxidative stress indices increase after MI [12, 13]. Acute coronary syndromes and MI alter biomarker levels including oxidative stress indices. Our findings should be confirmed by prospective studies.

Our results indicate that among patients with MI the severity of disease correlate with oxidative stress indices. The distribution of oxidative stress indices in extremely young smokers, without prior history of atherosclerosis, remains unknown. This study is particularly important since cigarette smoking is shown to increase the oxidative stress mediated vascular dysfunction in young adults [5]. Prior studies reported a strong correlation between oxidative stress and the presence of CAD in different patient subsets from the same population [14–16]. For instance, in an elderly population from Turkey (mean age 56 ± 8), Demirbag et al. [14] reported that TAS and TOS were significantly lower in CAD patients compared to control subjects. In that study the severity of CAD was assessed by using the Gensini score, and plasma and tissue TOS levels correlated positively with the Gensini score index.

We observed that lipid hydroperoxide levels (LOOH) were low and TOS levels were extremely high in young patients with MI. A correlation existed between the CAD severity and oxidative indices. Prior studies have evaluated lipid peroxidation (LOOH) in elderly patients with MI [12, 13]. In another clinical study from Turkey, Gur et al. [16], reported that LOOH levels are significantly elevated in patients with stable CAD as compared with healthy controls. LOOH levels negatively correlate with PON, ARE and TAS levels [14]. We report on young subjects with AMI, which may explain the differences in study findings. Studies have shown that LOOH and MDA play a role in predicting cardiovascular events in patients with stable CAD [17]. Similar to our study subjects, MDA levels are shown to be higher in premature CAD patients compared to older patients with CAD [18]. Prior studies included older subjects or patients with stable coronary disease.

LOOH may be a measure of atherosclerosis load, as observed in elderly patients [12, 13]. On the other hand, OSI, TOS and TAS may relate to hypercoagulable and inflammatory state in young patients with acute coronary syndromes.

The relationship between oxidative stress and CAD has long been a subject of clinical interest. Excessive oxidative stress and inadequate antioxidant defense can both induce early onset of severe CAD [19]. Elevated oxidative stress acts synergistically with the standard risk factors of CAD [20, 21]. The Turkish population has a high prevalence of smoking and of low HDLC [1, 2].

Diabetes mellitus was present in only 2 (3%) cases of our study population. On the other hand, heavy cigarette smoking was highly prevalent (79%). Therefore risk factor distribution displays unique characteristics in extremely young subjects with CAD.

Oxidative stress starts as result of a disturbed balance between reactive oxygen species and antioxidant defense. Increased oxidative stress plays a role in the onset of atherosclerotic cardiovascular disease [14–17]. We report that oxidative stress may exacerbate the onset and severity of CAD in extremely young smokers. Acute coronary syndromes and MI alter biomarker levels including oxidative stress indices. Our findings should be confirmed by prospective studies.

Standard CAD risk factors such as smoking, low HDLC, and diabetes mellitus can all alter oxidative indices [22]. Supporting our findings, circulating oxidized LDLC levels are found to correlate with the severity of CAD [23, 24]. Similarly, a number of studies have shown an association between the presence and severity of CAD and PON activity [16, 25, 26].

CAD is a complex disease with several genetic and environmental risk factors. The prevalence and duration of exposure to standard cardiovascular risk factors differ, depending on the age of disease onset. When CAD occurs at a mature age it is likely to be caused by long-standing exposure to standard risk criteria, such as diabetes mellitus. In contrast, premature CAD may involve novel risk factors, such as enhanced oxidative stress and inflammation.

Our study is cross-sectional and has several limitations. The sample size was small because of the lower prevalence of CAD in this group of patients. The majority of the patients were male, and we restricted our study to an extremely young population, after their first cardiovascular event. Therefore, it may not be possible to generalize our observations to the entire CAD population. Another limitation lies in the reproducibility of SYNTAX Scoring: we had three independent operators reviewing angiography findings. Since the study population included only very young subjects with MI, we selected age matched subjects without vascular history as the control group, which constitutes a limitation in the current study. We did not have clinical follow-up with these subjects. Future studies are needed with a larger sample size are needed to assess the additive effect of an OSI as a prognostic indicator in CAD. Standard CAD risk factors, diet, and physical activity can all affect oxidative stress [27]. Furthermore, CAD onset may be affected by ethnic variations between different populations. Disturbed or increased oxidative stress may

be an important contributor to vascular disease, particularly among very young, heavy smokers.

Conclusions

Oxidative stress parameters, such as OSI and TOS, associate positively with the severity of CAD in young heavy smokers. Future prospective studies in larger data sets from different populations are needed to confirm our observations. CAD is a complex disease. Several systems play a role in its onset and severity cigarette smoking remains highly prevalent among the young subjects in Turkey [2]. Acute coronary syndromes and MI alter biomarker levels including oxidative stress indices. Our findings should be confirmed by prospective studies. Our study may indicate potential mechanisms for explaining the increasing cardiovascular disease morbidity and mortality in developing countries.

Conflict of interest: none declared

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