Smoking is not Associated with Increased Ischemia-Modified Albumin Levels in Acute Coronary Syndrome

Özet
Amaç: Akut koroner sendrom, akut göğüs ağrısı ve miyokard iskemisinin başlı gelişiğin semptomları içeren klinik bir durumdur. İskemi modifiye albumin (IMA) son yıllarda AKS tanısında kullanılmaya başlanan yeni bir belirteçtir. İskemik durumunda oluşan reaktif oksijen radikallerinin IMA oluşumuna neden olduğu saptanmıştır. Bizim çalışmamızın amacı, yeni bir kardiyak iskemi belirteci olan IMA'nın AKS'deki düzeylerini tespit etmek ve reaktif oksijen radikallere neden olan sigara içiminin IMA düzeylerine etkisini ve bu etkinin, IMA düzeylerini değerlendirerek rolünü ortaya koymaktır. Gereç ve Yöntem: Tropinin I yüksekliği olmadan akut koroner sendrom tanı kriterleriene sahip 63 hasta ve yaş olarak benzer 61 kontrol bireyi bu çalışmaya katılmiştir. İskemi modifiye albumin düzeyleri kolorimetrik metot ile ölçülmüştür. Bulgular: Hasta grubundaki serum ischemia-modified albumin düzeyleri kontrol grubuna kıyasla anlamlı olarak yüksekti (Sırasıyla 0.644 ± 0.168 vs. 0.534 ± 0.116). Her ne kadar kontrol ve hasta grubunda sigara içenler daha yüksek ischemia-modifiye albumin düzeylerine sahip olsalar da bu fark istatistiksel olarak anlamalı değildir. Tartışma: Bu çalışmada, akut koroner sendromlu hastalarda sigara içiminin iskemi modifiye albumin düzeyleri üzerine hiçbir etkisinin olmadığını saptanmıştır.

Abstract
Aim: Acute coronary syndrome (ACS) is a clinical condition that exists signs and symptoms with acute chest pain and myocardial ischemia. Ischaemia-modified albumin (IMA) is a new diagnostic biochemical marker for acute coronary syndrome. It has been proposed that reactive oxygen species which occur in ischemia lead the formation of IMA. The aim of our study is to determine the levels of new cardiac ischemia marker IMA in ACS, the effect of smoking that is an event that leads to the formation of reactive oxygen species on IMA levels and the role of this effect on the interpretation of IMA results. Material and Method: 63 patients who met the acute coronary syndrome diagnosis criteria with no elevations of Tropinin I, and 61 age-matched control subjects were included in this study. Ischemia-modified albumin levels were determined with a colorimetric method. Results: Serum ischemia-modified albumin levels in the patient group were significantly higher compared to the control group (0.644 ± 0.168 vs. 0.534 ± 0.116). Her ne kadar kontrol ve hasta grubunda sigara içenler daha yüksek ischemia-modifiye albumin düzeylerine sahip olsalar da bu fark istatistiksel olarak anlamalı değildir. Tartışma: In this study, smoking was found to have no effect on ischemia-modified albumin levels in patients with acute coronary syndrome.

Keywords
Acute Coronary Syndrome; Ischemia; Risk Factor; Reactive Oxygen Species; Cardiovascular Death
Introduction

Acute coronary syndrome (ACS) is a clinical condition ranging from acute myocardial ischemia to myocardial necrosis, with symptoms developing related to these disorders [1]. Approximately 50% of both electrocardiography (ECG) and biochemical markers are not diagnostic at the time of presentation of the patients [2]. Due to the severity of the possible complications that might develop, it is crucial to diagnose these patients, prior to myocardial death, during the ischemic process.

The identification of structural changes in albumin lead to the finding of a newer cardiac ischemia marker, named ischemia modified albumin (IMA) [11]. The first step in the production of ischemia-modified albumin is ischemia-related hypoxia, which in turn results, in an increase, in reactive oxygen radicals, and finally in a change, in the N-terminal of albumin [3].

The most important cause of IMA production is the reactive oxygen radicals, which result in the change of the structure of albumin. Especially the hydroxyl-radical, among the reactive oxygen radicals, has been found to be effective in the production of IMA. Free oxygen radicals decrease the metal ion binding capacity of the N-terminal of albumin by performing structural changes in this region of the molecule [3]. High IMA values are seen in end stage renal failure [4], intestinal ischemia [5], cerebrovascular ischemia [6]. In addition, IMA has been reported to be an indicator of oxidative stress, as well [7]. Smoking is the main risk factor for both ACS and coronary artery disease (CAD). Smoking has been known to cause reactive oxygen radical production [8]. Reactive oxygen radicals together with smoking in association with increased oxidative stress increase the risk of atherosclerosis and coronary heart disease [9]. There are no studies in the literature on how the reactive oxygen radicals formed due to smoking affect IMA levels.

The aim of this study is to determine the effects of acute coronary syndrome and smoking which causes the production of reactive oxygen species in patients with acute coronary syndrome to ischemia-modified albumin levels.

Material and Method

Study Population

After obtaining the approval of the local ethics committee with number 483 on 27/11/2008, 63 patients with a definitive diagnosis of ACS according to European Society of Cardiology and American College of Cardiology (ESC/ACC) criteria, whose troponin levels measured for the first time at admission were normal among patients who presented with chest pain, and 61 healthy individuals similar to the patient group in terms of age and gender were included in the study.

Blood samples, 8 mL each, drawn from the patients, who presented to the emergency department with chest pain for biochemical measurements, in pure gel tubes were centrifuged at 4000 cycles/min for 5 minutes after waiting for 30 minutes for clot formation. After routine measurements of cTnI and biochemical measurements, serum samples were stored at -20°C for later IMA and albumin measurements.

Groups comprised of patients with ACS, and healthy individuals were separated into two groups each according to the WHO criteria for smoking. According to these criteria, individuals who smoke at least one cigarette per day for six months or more and continued to smoke were accepted as smokers, and others were accepted as non-smokers [10].

Anamnesis of all the patients included in the study, information about ECG with 12 derivations, vital findings (blood pressure and heart rate), demographics (age, gender, etc...) and smoking status were recorded.

Standard (25 mm/sec rates, 10 mm/mV amplitude) ECG with 12 derivations of all patients that presented to the emergency department with chest pain were obtained. ST-T segment changes in two or more derivations in the ECG obtained were accepted as a positive ECG finding.

Pregnant women, patients with cerebrovascular disease, peripheral vascular disease, renal failure, acute abdomen, and patients who had an albumin level of less than 3 g/dL or greater than 5.5 g/dL were excluded from the study. A written informed consent was given to all participants, and this study was approved by local ethic committee.

Biochemical Measurements

Measurements of cardiac troponin I (cTnI) were performed in an ADVIA Centaur CP auto-analyzer, using the three region sandwich immune test with direct chemilumimetric technology (Lot: 38259033, Ref: 02790309).

Albumin measurements were performed in an Architect C16000 (Abbott Diagnostic,USA) auto-analyzer, using the bromocresol green method (Lot: 70040HW00, Ref: 7D53-20).

IMA levels were determined according to Bar O et al [11]. Briefly, after adding 50 µl of 0.1% cobalt chloride to 200 µl of the patient’s serum, the mixture was vortexed and incubated for 10 minutes to allow for the formation of albumin cobalt binding. After incubation, 50 µl of Dithiothreitol (DTT) in a concentration of 1.5 mg/mL was added to the mixture to produce a color reaction with cobalt, which was not bound to albumin and it was allowed to incubate for two minutes. One mL of 0.9% NaCl was added to the mixture after two minutes, and the reaction was completed. At the end of the reactions, the difference in the absorbance (ABSU) values between the samples and blind samples was recorded as IMA values. The intra-assay CV value and inter-assay CV value were determined as 3.20% and 3.91%, respectively.

Statistical Analysis

Calculations and statistical analysis were performed using the SPSS 15.0 statistical program. Results were given as mean ± standard deviation with a 95% confidence interval. Differences between the groups were evaluated with independent t-test and values of p<0.05 were accepted as significant.

Results

A total of 124 subjects, comprised of 63 patients with ACS and 61 healthy individuals, were included in the study. Demographic data and the results of biochemical measurements are presented in Table 1.

Mean age of the individuals included in the control group was 59.19 ± 11.03 years, while it was 60.73 ± 12.76 years in the ACS group. The difference in mean age between the two groups was not found to be statistically significant (p=0.475).

Systolic and diastolic blood pressure values of the individuals included in the study at the time of admission to the emergency department with chest pain were obtained.
service department were 131.86 ± 19.06 mm/Hg and 78.75 ± 11.35 mm/Hg in the control group, respectively, and 137.87 ± 27.63 mm/Hg and 76.20 ± 13.51 mm/Hg in the ACS group, respectively, and no statistically significant differences were found between the control and ACS groups (Table 1).

Albunin levels measured in the control and ACS groups were 4.52 ± 0.30 g/dL and 4.56 ± 0.31 g/dL, respectively, and no significant difference was determined between the two groups in the albumin levels (p=0.451) (Table 1).

Table I. Demographic characteristics and biochemical values of study participants

| Control Group (n=63) | ACS (n=65) | p |
|---------------------|-----------|---|
| Gender (M/F)        | 47 / 14   | 49 / 14 |
| Age (years)         | 59.19 ± 11.03 | 60.73 ± 12.76 | 0.475 |
| SBP (mm/Hg)         | 131.86 ± 19.06 | 137.87 ± 27.63 | 0.163 |
| DBP (mm/Hg)         | 78.73 ± 11.35 | 76.20 ± 13.51 | 0.262 |
| Albumin (g/dL)      | 4.52 ± 0.30 | 4.56 ± 0.31 | 0.451 |
| IMA (ABSU)          | 0.534 ± 0.116 | 0.644 ± 0.168 | <0.001* |

IMA, Acute coronary syndrome; M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure; IMA, ischemia-modified albumin; ABSU, absorbance unit; n, number of participants. Results are presented as mean ±SD. *=statistically significant

IMA levels were 0.534 ± 0.116 ABSU and 0.644 ± 0.168 ABSU in the control and ACS groups, respectively, with a statistically significant difference between the groups (p=0.000) (Table 1). Pearson’s correlation tests were performed to demonstrate a correlation between albumin and IMA levels between the control and ACS groups. No correlation was determined between albumin and IMA levels in the control group (p=0.290, r = 0.138). Similarly, no correlation was determined between albumin and IMA values in the ACS group, either (p=0.643, r = -0.060).

To evaluate the effects of smoking on IMA levels, the control and ACS groups were separated into smokers and non-smokers. The control group included 31 non-smokers (19 males) and 30 smokers (28 males), and the ACS group included 33 smokers (21 males) and 30 smokers (28 males). Data of both groups are demonstrated in Table 2 and Table 3.

In each group, the mean ages between smokers and non-smokers were statistically different (Table 2, Table 3). The measured albumin levels in the two groups of smokers and non-smokers were 4.59 ± 0.27 g/dL and 4.45 ± 0.33 g/dL in the control group (p=0.087), respectively, and 4.53 ± 0.31 g/dL and 4.59 ± 0.30 g/dL in the ACS group (p=0.457), respectively. The measured IMA levels in the two groups of cigarette smokers and non-smokers were 0.549 ± 0.110 ABSU and 0.521 ± 0.121 ABSU (p=0.348), respectively in the control group and 0.659 ± 0.164 ABSU and 0.630 ± 0.173 ABSU, respectively in the ACS group (p=0.498), with no statistical significance between the groups.

When the IMA levels were evaluated in the groups according to the time interval passed after the last cigarette, the IMA levels among the cigarette smokers in the control group were as follows: mean IMA levels in individuals who smoked the last cigarette less than three hours before blood was drawn (n=16) was 0.544 ± 0.112 ABSU, and 0.554 ± 0.110 ABSU in individuals who had last smoked a cigarette three hours or more (n=14) before the blood was drawn. No statistical significance was determined between the groups (p=0.794).

The IMA levels among the cigarette smokers in the ACS group were as follows: mean IMA levels in individuals who smoked the last cigarette less than three hours before the blood was drawn (n=17) was 0.631 ± 0.167 ABSU, and 0.696 ± 0.159 ABSU in individuals who last smoked a cigarette three hours or more (n=13) before the blood was drawn. No statistical significance was determined between the groups (p=0.293).

In the evaluation of past medical history of the patients in the ACS group, 14 patients had no known disease and 49 patients were identified to have one or more comorbid diseases. Among the patients with additional illnesses, 36 had hypertension, 15 had diabetes, 23 had coronary artery disease, and 7 had lipid metabolism disorder. When the t-test was performed to evaluate the effect of co-morbid disorders on IMA levels, no statistical differences were found (p=0.734).

The duration of pain in 42 patients among those that presented with chest pain to the emergency department was less than three hours, and it was more than three hours in 21 of the patients. When the IMA levels were compared in patients with two different groups of duration of chest pain, no statistically significant differences were found between the groups (p=0.768).

Among the patients that presented to the emergency department with chest pain, 42 patients described typical chest pain, while 21 patients had described atypical chest pain. No statistically significant difference was found in the IMA levels between the patients with typical and atypical chest pain (p=0.768).

Among patients that presented to the emergency department with ST-T changes in two or more derivations in the ECG were accepted as having a positive ECG finding, 35 patients had a positive ECG finding and 28 had no diagnostic ECG finding. Statistically significant difference was not found in the IMA levels between the patients with positive and negative ECG findings (p=0.512).

The definitive diagnosis of the patients was unstable angina

Table II. Biochemical and demographic results of control subjects according to classification of smoking status.

| Control Group (n=61) | p |
|---------------------|---|
| Gender (M/F)        | 19/12 |
| Age (years)         | 66.19 ± 9.40 |
| Albumin (g/dL)      | 4.45 ± 0.33 |
| IMA (ABSU)          | 0.521 ± 0.121 |

Non-smokers (n=33) | Smokers (n=30) |
|-------------------|----------------|
| Gender (M/F)      | 28/2 |
| Age (years)       | 65.30 ± 9.05 |
| Albumin (g/dL)    | 4.59 ± 0.27 |
| IMA (ABSU)        | 0.549 ± 0.110 |

M, male; F, female; IMA, ischemia-modified albumin; ABSU, absorbance unit; n, number of participants. Results are presented as mean ±SD. *=statistically significant

Table III. Biochemical and demographic results of acute coronary syndrome patients according to classification of smoking status.

| ACS (n=63) | p |
|-----------|---|
| Gender (M/F) | 21/12 |
| Age (years)  | 66.90 ± 11.39 |
| Albumin (g/dL) | 4.59 ± 0.30 |
| IMA (ABSU)   | 0.630 ± 0.173 |

Non-smokers (n=33) | Smokers (n=30) |
|-------------------|----------------|
| Gender (M/F)      | 28/2 |
| Age (years)       | 53.93 ± 10.66 |
| Albumin (g/dL)    | 4.53 ± 0.31 |
| IMA (ABSU)        | 0.659 ± 0.164 |

ACS, Acute coronary syndrome; M, male; F, female; IMA, ischemia-modified albumin; ABSU, absorbance unit; n, number of participants. Results are presented as mean ±SD. *=statistically significant
pectoris (USAP) in 42 patients and AMI (NSTEMI 9, STEMI 12) in 21 patients. Statistically significant difference was not found in the IMA levels between the patients with USAP or AMI as a definitive diagnosis (p=0.540).

Discussion
In patients presenting with chest pain to emergency services, the first diagnoses to be ruled out are acute coronary syndromes [12]. IMA is a biochemical marker that has been frequently emphasized lately, which has been approved by Food and Drug Administration (FDA) to be used in demonstrating myocardial ischemia [13]. IMA has been suggested to be an early marker in the diagnosis of ACS in patients with non-diagnostic ECG and cardiac marker results at the time of presentation to the emergency services [14]. In this study, among patients presenting to the emergency department with chest pain with normal cTnI values, who were later diagnosed with ACS during follow-up, had significantly greater IMA levels compared to the control group, which was similar to the literature data [15,16]. This suggests that increased IMA levels can be beneficial in diagnosing ACS.

Cigarette smoking is a significant risk factor in the development of CAD and ACS, and is known to increase the oxidative burden on the body and the production of reactive oxygen radicals with its acute effects [17]. Theoretically, reactive oxygen radicals originating due to cigarette smoking might result in IMA formation similar to the course of ischemia. No data exist in the literature on the effects of cigarette smoking on IMA levels. Although the IMA levels were found to be increased in cigarette smokers compared to non-smokers in the current study, the difference between the groups was not statistically significant. The mean age was found to be statistically significantly higher in the non-smoking group compared to smokers. In one study, age demonstrated no effect on IMA levels; therefore, this difference was not taken into account [18]. Individuals were grouped according to the last cigarette smoked, since it was believed that the time passed after the last cigarette smoked could affect IMA levels. Groups were determined with a cut-off point of three hours between the cigarette smoking and presentation to the emergency department, since IMA has been reported to return to normal levels in three hours in the previous studies [19]. The amount of time that passed after the last cigarette was smoked was found to have no effect on IMA levels. A suggestion to explain this is that reactive oxygen radicals produced due to cigarette smoking might be less than the reactive oxygen radical concentration produced during myocardial ischemia. However, one limitation of this study is that serum reactive oxygen radical measurements were not performed. In addition, when the fact that some conditions, such as increases in local acidosi and free fatty acid levels produced during ischemia, might also cause an increase in IMA levels are taken into account, we suggest that the reactive oxygen radicals as a result of cigarette smoking are not the only cause of IMA production, instead, they are the result of a series of complex events.

Diabetes and hypertension are important risk factors for CAD and ACS [17]. However, there is no data in the literature on whether there are any changes in the IMA levels due to these additional disorders in cases of ACS developed in patients with these additional comorbidities. In the current study, IMA levels in ACS were found to be similar in patients with and without concomitant disease as a risk factor for ACS. A significant difference could not be determined in IMA levels, in patients with chest pain with a duration of more than three hours and less than three hours. Although IMA was identified to return to normal levels in three hours in Percutaneous transluminal coronary angioplasty (PTCA) application, which is an in-vivo myocardial ischemia model, the ischemia produced in these models are transient, and the ischemic process ends at the end of PTCA [19]. Because the chest pain developed in ACS is due to myocardial ischemia, the ischemic process, and thus the production of IMA, continues in patients presenting to emergency services with chest pain. Therefore, the identification of increased IMA levels in patients presenting to emergency services with chest pain, regardless of the duration of the complaint, can be accepted as a sign suggesting the presence of ACS.

Atypical chest pain complicates the process of performing a diagnosis [12]. IMA levels have been reported to have an independently high sensitivity in diagnosing ACS in patients presenting to emergency services with chest pain, even if their ECG findings are non-diagnostic [18]. No significant differences were found between the IMA levels among patients without diagnostic ECG and with positive ECG findings. This suggests that the identification of high IMA levels in patients with chest pain in the emergency services might be due to ACS, even though their ECG findings are non-diagnostic.

Sinha et al. demonstrated significantly higher IMA levels in patients with USAP compared to patients with AMI [20]. On the contrary, Roy et al. found no differences in the IMA levels among patients with USAP or AMI [14]. We could not demonstrate any differences in the measured IMA levels between patients diagnosed with USAP and AMI among the patients with a definitive diagnosis of ACS. Increased IMA cannot differentiate USAP and AMI among individuals with normal cTnI levels. This might be due to the fact that the process of ischemia is common in both USAP and AMI before the cell death.

The low number of subjects when the cigarette smokers in this study were further divided into groups according to the last cigarette smoked might be a limitation of this study. Also, the duration of cigarette smoking is unknown in this study and this may also be evaluated as a limitation.

In conclusion, the relation of IMA, which is a new biochemical marker recently introduced into practice, and cigarette smoking is evaluated for the first time, and it was demonstrated that cigarette smoking does not affect IMA levels. In addition, the use of IMA for the diagnosis of ACS, in accordance with the literature, was found to be beneficial. IMA levels were not found to be related to past medical history, ECG findings, and the nature and duration of chest pain of the patients, and thus, the variables should not be taken into account in evaluating the results of IMA in patients with the suspicion of ACS. Since IMA is a new biomarker, there are limited data about its interactions. The evaluation of IMA levels in the case of the production of free oxygen radicals, which affect IMA formation, will be helpful in disclosing the interaction of this marker.
Acknowledgements

No funding from any pharmaceutical firm was received for this project, and the authors’ time on this project was supported by their respective employers.

Competing interests

The authors declare that they have no competing interests.

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