Pregnancy-associated plasma protein A and procalcitonin as markers of myocardial injury in patients with acute coronary syndrome

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1. Introduction
Diagnosis of patients with acute coronary syndrome is important in the emergency department. Diagnosis usually is established with clinical findings, electrocardiographic changes, biochemical markers of myocardial damage, and myocardial perfusion imaging. There are no ideal biochemical markers to quantify myocardial damage early after acute coronary syndrome with high clinical sensitivity and specificity. Although cardiac troponin levels are highly sensitive and specific markers for the diagnosis of myocardial necrosis, troponin may not be detected in the blood until 6 to 9 h after the onset of chest pain (1). Therefore, other early markers of myocardial necrosis are being evaluated.

Pregnancy-associated plasma protein A (PAPP-A), a metalloproteinase present in the serum of women in late pregnancy, is a marker of inflammation and plaque instability (2). PAPP-A is a useful marker for early detection of acute coronary syndrome and identification of patients at risk for an acute ischemic cardiac event (3–5). Another serum protein, ischemia-modified albumin (IMA), increases rapidly in acute ischemic coronary events and may be a sensitive marker for the diagnosis of myocardial ischemia (6,7).

Procalcitonin, a calcitonin precursor hormone secreted by the thyroid gland, has high serum levels in inflammatory conditions. High procalcitonin levels are correlated with the severity of infections. Follow-up is an important marker for the diagnosis and treatment of bacterial sepsis (8). There are few studies about serum procalcitonin levels in patients with cardiogenic shock and acute coronary syndrome, and results are conflicting. Although procalcitonin levels may be increased in patients with acute coronary syndrome on admission to the hospital, procalcitonin levels may also be normal in patients who have uncomplicated acute myocardial infarction (9,10). A literature review showed no previous study comparing PAPP-A, IMA, procalcitonin, and troponin I levels on admission of patients with acute coronary syndrome to the emergency department.
We performed the present study to evaluate the hypothesis that PAPP-A, IMA, and procalcitonin may be useful in the diagnosis of acute coronary syndrome. The purpose of this study was to evaluate PAPP-A, IMA, procalcitonin, and troponin I levels on admission of patients with acute coronary syndrome to the emergency department.

2. Materials and methods
Between 1 June 2011 and 31 October 2012, there were 100 patients aged 18 to 80 years who were diagnosed with acute coronary syndrome (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina pectoris) at the Emergency Department of the Faculty of Medicine of Selçuk University and recruited for the study group. Ischemic character chest pain, ECG findings (ST elevation or depression, ST-segment depression, T wave changes, newly developed left bundle branch block) and high troponin I level were criteria for the diagnosis of acute coronary syndrome. Acute coronary syndrome was diagnosed when the two criteria were positive. A control group of 100 healthy volunteers aged 18 to 80 years included individuals recruited from the Emergency Department who did not have acute coronary syndrome. Patients with history of heart failure, systemic infection, malignancy, pregnancy, acute or chronic renal failure, acute or chronic liver failure, stroke, endocrine disease, oncological disease, chronic obstructive pulmonary disease, trauma were excluded from the control group. Patients were excluded from the study group if they had a history of severe systemic disease, stroke, endocrine disorders, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, acute or chronic infection, sepsis, trauma, pregnancy, or malignancy. Patients and control subjects were informed about the study and gave written informed consent. The study was approved by the Selçuk University Faculty of Medicine Non-Drug-Using Clinical Research Ethics Committee (No. 2011/051).

2.1. Study setting
Venous blood samples were taken from patients in the study group within 6 h after the onset of ischemic chest pain.

In all subjects, venous blood samples were drawn into straight jelly tubes during the evaluation in the emergency department for evaluation of PAPP-A, IMA, procalcitonin, and troponin I. After 25 min, the samples were centrifuged at 3000 rpm for 5 min, and sera were stored at –80 °C until they were thawed to room temperature for testing. The PAPP-A and procalcitonin levels were determined from sera with commercially available kits (Roche Cobas kits, Roche, Japan) and an analyzer (Roche Modular E170 device, Roche) that was calibrated and checked with its own calibrator and controls.

The IMA level was measured as the binding capacity of reduced cobalt to albumin using a rapid colorimetric method (11). Each serum sample (200 µL) was added to a glass tube and mixed with cobalt chloride (0.1% in water; 50 µL; Merck, Germany). After gentle shaking, the mixture was left undisturbed for 10 min to ensure sufficient binding of cobalt to albumin. Dithiothreitol (1.5 mg/µL; 50 µL; Merck) was added as a coloring agent; a control specimen was prepared for each sample using distilled water (50 µL) instead of dithiothreitol. After 2 min, sodium chloride (0.9%; 1 µL) was added to stop the binding between cobalt and albumin. Absorbance at 470 nm was measured with a spectrophotometer (PerkinElmer Lambda 25 UV/VIS spectrometer, Lot No: L600000B, Serial No: 501S10083108, PerkinElmer, USA). Color formation was compared between specimens with dithiothreitol and controls, and the results were expressed as absorbance units. The albumin-adjusted IMA levels were calculated as previously described and expressed as (individual serum albumin concentration/median albumin concentration of the population) × IMA value (12). All samples were measured during the same laboratory session. The intraassay coefficient of variation was 7.1%, consistent with information from Abbots (Japan). Albumin concentrations were determined with a commercially available kit (Merck) based on the bromocresol purple method.

2.2. Data analysis
The Shapiro–Wilk test showed that the markers had nonparametric distributions. The Mann–Whitney test was used to compare medians. Spearman rank correlation was used to evaluate the relation between the markers. Data were reported as mean ± SD. Statistical significance was defined as P ≤ 0.05.

3. Results
The data related to risk factors of the patient and control groups are shown in Table 1.

Sixty-four patients with acute coronary syndrome had ST-segment elevation myocardial infarction (STEMI). In the acute coronary syndrome group, 31 patients had non-ST-segment elevation myocardial infarction (NSTEMI) and 5 patients had unstable angina pectoris (UAP). The mean time from the beginning of ischemic chest pain until a venous blood sample was taken in the patients with acute coronary syndrome was 115 ± 72 min.

The mean serum PAPP-A, procalcitonin, and troponin I levels of the patients with STEMI were significantly greater than those of the control group (P < 0.01). The mean serum PAPP-A, procalcitonin, and troponin I levels of the patients with NSTEMI were significantly greater than those of the control group (P < 0.01). A significant difference was not determined between patients with UAP and the control group for mean serum PAPP-A, procalcitonin, and troponin I levels (Table 2).
The mean age was similar between patients with acute coronary syndrome and control subjects (Table 3). The mean serum PAPP-A, procalcitonin, and troponin I levels were significantly greater in patients with acute coronary syndrome than control subjects (Table 3). The mean IMA level was similar between patients with acute coronary syndrome and control subjects (Table 3). There were no significant correlations between PAPP-A levels and IMA, procalcitonin, or troponin I levels in patients with acute coronary syndrome.

4. Discussion

The present study showed that PAPP-A, procalcitonin, and troponin I levels were increased in patients with acute coronary syndrome (Table 1), consistent with the hypothesis that these markers may be useful diagnostically. However, IMA was not increased in patients with acute coronary syndrome (Table 1).

The present study confirmed previously reported findings that PAPP-A may be a useful diagnostic marker for acute coronary syndrome. In a previous study that compared PAPP-A levels with troponin I and creatine kinase-MB fraction in the early diagnosis of acute coronary syndrome, PAPP-A had high diagnostic sensitivity (90%) and specificity (85%) (2). Furthermore, PAPP-A was a useful marker in the clinical evaluation of patients with acute coronary syndrome (4). In addition, studies to evaluate PAPP-A for risk assessment and prognosis showed that PAPP-A was associated with recurrent cardiovascular events and mortality in patients with STEMI and NSTEMI (13–15). In patients with ischemic cardiac chest pain, high PAPP-A levels may be helpful in predicting long-term cardiovascular mortality (3).

Although PAPP-A, procalcitonin, and troponin I levels were all elevated in patients with acute coronary syndrome (Table 1), no correlation was evident between PAPP-A levels and IMA, procalcitonin, or troponin I levels in patients with acute coronary syndrome. Therefore, PAPP-A levels may be a useful indicator of myocardial necrosis for the diagnosis of acute coronary syndrome but may follow a different time course than procalcitonin or troponin I.

In the present study, mean IMA levels were similar between patients who had acute coronary syndrome and control subjects. This suggests that IMA levels may not be useful as a diagnostic indicator in the differential diagnosis of acute coronary syndrome in the emergency department. Previous studies reported that IMA had good accuracy (66% to 95%) but low specificity (13% to 45%) for the diagnosis of patients with acute coronary syndrome (16–18), although IMA may not be used to reliably exclude the diagnosis of acute coronary syndrome in the emergency department (19,20). IMA may be a guide as to whether to perform further investigation for acute coronary syndrome in patients admitted to the emergency department with chest pain, analogous to D-dimer testing in the diagnostic algorithm for pulmonary embolism (21,22). In addition, IMA levels may not distinguish between patients who have either ST-segment elevation myocardial infarction or unstable angina pectoris (23).

In the present study, procalcitonin levels were significantly higher in patients with acute coronary syndrome on admission to the emergency department than healthy control subjects (Table 1), but there was no correlation between procalcitonin and troponin I levels. Therefore, elevated procalcitonin levels in patients with acute coronary syndrome on admission to the emergency department may be a supportive diagnostic indicator, and high procalcitonin levels may reflect the severity of the inflammatory process in patients with acute coronary syndrome.

Few previous studies have been performed to evaluate procalcitonin levels in patients with acute coronary syndrome, and conflicting results were reported. In a study of patients

<table>
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<tr>
<td>Age</td>
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*NS, Not significant; P > 0.05.

Table 1. Risk factors related to acute coronary syndrome in patient and control groups.
admitted to the hospital with acute myocardial infarction, serum procalcitonin levels had increased before troponin I and creatine kinase-MB fraction levels, and procalcitonin was considered a new and precise indicator for the diagnosis of acute myocardial infarction (9). However, another study concluded that procalcitonin levels had increased only in patients with cardiogenic shock from acute myocardial infarction and in few patients with uncomplicated STEMI; indicators of inflammation such as C-reactive protein were considered more valuable and were not correlated with procalcitonin levels (24). Nevertheless, elevated procalcitonin levels on admission may be associated with short- and long-term mortality in patients who have acute coronary syndrome without signs of infection and who are followed in a coronary intensive care unit, and procalcitonin levels potentially may be an indicator to identify patients at high risk of mortality from acute coronary syndrome (25).

Limitations of the present study include the unavailability of information about time between onset of symptoms and admission to the emergency department for patients with acute coronary syndrome; this information may have improved the potential for identifying a correlation between the measured markers. In addition, only one blood sample was available for each patient, which precluded an evaluation of the time dependence and peak level of the markers. Furthermore, the PAPP-A, IMA, procalcitonin, and troponin I levels were evaluated only for use in emergency differential diagnosis, and follow-up information was not available to evaluate these markers for prediction of prognosis. Nevertheless, the present results justify further study to evaluate these important issues.

In summary, the present results provide evidence that PAPP-A, procalcitonin, and troponin I levels may be useful, but IMA level may not be helpful, in the diagnosis of acute coronary syndrome in patients admitted to the emergency department.

Acknowledgment

This study was supported by the Selçuk Üniversitesi Bilimsel Araştırma Projeleri Koordinatörlüğü.

References


