Correlation of c-reactive protein and serum iron levels with syntax score

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Abstract:

Objectives: Cardiovascular diseases are one of the most common causes of morbidity and mortality in the world. Atherosclerosis is an inflammatory process. Serum C-reactive protein (CRP), is an acute-phase protein rises in response to inflammation. Serum iron (Fe) is one of the essential metals to human body. Inflammation and infection are characterized by changes in Fe metabolism. Since atherosclerosis is an inflammatory process, changes in CRP and serum iron levels are expected. However, the distribution of the disease in the coronary arteries is important for mortality and morbidity. The distribution of the disease can be determined by syntax score.

Materials and methods: The study included 407 patients (56.4±10.7 years, 51.4% males). In the study 53 patients had critical lesions and 354 had no critical lesions. According to the baseline coronary angiograms, syntax score was calculated in all patients. The laboratory variables including hemoglobin levels, blood glucose, creatinine, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), Fe, and CRP were studied.

Results: In laboratory parameters of all groups CRP levels mean 0.75±1.8mg/dl, Fe mean 80.4±27.5mg/dl and syntax score mean 1.5±4.8 were calculated. High syntax score levels correlated with Fe and CRP levels.

Conclusions: The findings of the present study showed elevated serum iron and CRP concentrations to be associated with increased syntax score and atherosclerosis severity.

Keywords: Atherosclerosis; C-reactive protein; serum iron; syntax score

Introduction:

Cardiovascular diseases are one of the most common causes of morbidity and mortality in the world. Cardiovascular disease is epidemic at present and it is the single most important disease in the world in terms of mortality, morbidity, disability, and economic loss. This chronic disease has also an enormous impact on the quality of life. There are lots of risk factors in cardiovascular disease such as hyperlipidemia, hypertension, cigarette smoking, obesity, diabetes mellitus and a positive family history of cardiovascular disease. Some risk factors can be changed by lifestyle change. We can eliminate most risk factors with a change in diet.

Serum C-reactive protein (CRP), an acute-phase protein of hepatic origin, rises in response to inflammation. C-reactive protein (CRP) is an established marker of systemic inflammation. An elevation of serum CRP level lacks specificity, but, as a biomarker, it has been implicated in a variety of illnesses, including rheumatoid arthritis, sepsis, and, more recently, atherosclerosis (Pepys et al., 1985). CRP use in stable coronary disease. After an acute cardiac
event, CRP remains elevated for several months. In the ECAT study, increase in CRP was associated with an increase in cardiac events by 50%. CRP, in conjunction with two other markers, N-terminal pro-brain natriuretic peptide and cystatin C, was shown to be a risk factor for cardiovascular and total cause mortality (Zelhelius et al., 2008). Atherosclerosis is a disease characterized by widespread endothelial inflammation. CVD is mainly caused by atherosclerosis, which starts from lipid infiltration in the vessel wall, endothelial dysfunction, and chronic low-grade inflammation causing plaque development that ends with clinical ischemic complications. Levels of CRP in serum ≥3 µg/mL are used in the clinical setting as unspecific marker for inflammation, infection, and tissue injury, associated with an acute-phase response (Koenig et al., 2008). Indeed, CRP is considered a predictor of future cardiovascular events (Kapteg et al., 2012).

Atherosclerosis is a complex inflammatory pathological process initiated by lipid deposition in the arterial wall with a subsequent recruitment of circulating leukocytes. C-reactive protein contributes to endothelial dysfunction and hypertension by inhibiting nitric oxide (Verma et al., 2002), increasing endothelin-1 production, and thus impairing endothelium-dependent vascular relaxation (Guan et al., 2009).

Serum iron (Fe) is one of the essential metals to human body. In fact, if from one side this metal is essential to almost all organisms, on the other, it becomes toxic when accumulating above certain thresholds. The ability of Fe to stably interconvert between the most common oxidative forms Fe²⁺ and Fe³⁺ favors its participation into the Fenton reaction and the generation of highly reactive hydroxyl radicals. These subsequently damage DNA, lipids and proteins, causing cells to undergo Fe-mediated oxidative stress and programmed cell death. Thus, maintaining Fe homeostasis is a necessary step for the correct cell functioning and to prevent Fe-mediated tissue damage (Gozzelino et al., 2010). Inflammation and infection are characterized by changes in Fe metabolism, a cross-talk facilitated by the presence of binding sites for proinflammatory cytokines in the promoter of genes regulating Fe homeostasis. For the first time, Sullivan (Sullivan, 1981) suggested that iron stores in human body may be positively correlated with the risk of coronary heart disease. According to his hypothesis, production of free radicals that are subsequently modified to low density lipoprotein cholesterol (LDL) is important in the development of atherosclerosis and iron may stimulate the catalyzing of oxidation reactions that produce free radicals (Sempos et al., 1996; Meyers, 1996). And also serum iron levels correlated with inflammation. We all know about that atherosclerosis is an inflammatory process.

The syntax (Synergy between PCI with TAXUS and Cardiac Surgery) score (SS), which is an angiographic tool used in grading the complexity of CAD, is assessed according to the coronary anatomy and characteristics of the coronary lesion. Clinical studies have shown that SS has prognostic importance in CAD and provides important information regarding the selection of revascularization strategy. (Serruys et al., 2009a; Valgimigli et al., 2007) Because CAD is an essential inflammatory disease, we hypothesized that CRP and Fe levels could be associated with complexity of CAD as assessed by SS. This study aimed to assess the relationship between CRP and Fe levels and the severity of coronary atherosclerosis assessed by SS in patients with stable CAD.

Methods:

2.1 Study population

We enrolled 407 consecutive patients with stable angina pectoris (SAP) who underwent coronary angiography for suspected CAD. The patients with a history of coronary artery bypass graft surgery or percutaneous coronary intervention, malignancy, active infection, and connective tissue disorder were excluded from the study. Our local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki.
2.2 | Laboratory measurements
Blood samples were collected before the index coronary angiography after an overnight fast and analyzed in the laboratory of our institution. The laboratory variables including hemoglobin levels, blood glucose, creatinine, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), Fe, and CRP were studied. Normal ranges were 0.0-0.80 mg/dL for CRP, 60 – 180 mg/dL for Fe.

2.3 | Angiographic analysis
All patients underwent coronary angiography via standard Judkins technique. Selective coronary angiograms were recorded using a digital angiographic system (Dicom-viewer; MedCom GmbH, Darmstadt, Germany) for quantitative analysis. According to the baseline coronary angiograms, SS was calculated in all patients by two experienced cardiologists who were blinded to all other data. The SS was determined for each coronary lesion producing >50% diameter stenosis in vessels >1.5 mm, based on the SS calculator. Lesions over 70 percent were considered critical.

2.4 | Statistical analyses
Data were represented as mean ± standard deviation or median for quantitative variables and counts or percentage for categorical variables. Differences between 2 groups were tested with a t test or Mann-Whitney U test for continuous variables and chi-square or Fisher’s exact tests as appropriate for categorical variables. Multivariate logistic regression (stepwise backward conditional analysis) was used to determine independent predictors of intermediate-high SS group using variables that were found to be significant in univariate analysis (P < .05). The data were analyzed using SPSS version 23.0 (SPSS Inc., Chicago, Illinois)

Results:
The study included 407 patients (56.4± 10.7 years, 51.4% males). The SS ranged from 0.0 to 31, with a mean of 1.5 ± 4.8. In the study 53 patients had critical lesions and 354 had no critical lesions. The baseline characteristics of the patients are shown in Table 1. In our study in our patient groups there weren’t any significant differences in diabetes mellitus, hypertension. In no critical lesions group 73 patients had diabetes mellitus and in critical lesions group 14 patients had diabetes mellitus, not differ each other. Similiary in no critical lesions group 162 patients had hypertension and in critical lesions group 136 patients had hypertension, not differ each other. In laboratory parameters glucose, creatine, LDL, triglyceride, CRP and serum iron levels were measured. In groups CRP and serum iron had differences in groups. SS were also differed each other. We also found that SS and CRP, serum iron level correlated. In our study, high SS level and increase in serum iron levels and CRP levels are remarkable. (Table 2)

Discussions:
CAD is a leading cause of mortality, morbidity, and disability. CAD has been associated with several risk factors, including sex, age, elevated blood cholesterol, diabetes mellitus, cigarette smoking, hypertension, and atherosclerosis. In this study, a significant difference was found between serum iron and CRP levels in patients with and without critical coronary lesions and also in present study indicated that C-reactive protein and serum iron levels were significantly associated with SS. The SS accounts for the number and the location of the coronary lesion and thus tries to determine the myocardium under the risk of ischemia. Numerous validation studies since the syntax trial confirm that SS is an independent predictor of short-and long-
term morbidity and mortality and adverse cardiovascular outcomes in a wide range of patients, including stable CAD (Serruys et al., 2009b; Garg et al., 2010; Van Gaal et al., 2009). Inflammation plays an important role in all stages of atherosclerosis (Drakopoulou et al., 2009). CRP and serum iron are markers of inflammation that are frequently used in clinical practice. Serum CRP, an acute phase protein from the liver, is elevated in response to inflammation and improved risk prediction for patients with CAD (Koenig, 2013). In addition, high CRP levels have been shown to be associated with the severity of coronary involvement in patients with stable CAD (Pan et al., 2015). Although the physiopathogenesis of the relationship between CRP and CAD severity is not fully understood, multiple mechanisms may be involved. CRP has been shown to impair the endothelial progenitor cells, impair fibrinolysis, increase collagen degradation in monocytes, activate the complement system, and may be involved in the uptake of LDL-C by macrophages and turning them into foam cells (Bisoendial et al., 2010; Jialal et al., 2004; Devaraj et al., 2009). In our study, CRP levels, atherosclerosis and syntax score correlated means that severity, and complexity of coronary atherosclerosis increases in high CRP levels.

Several trace elements have also been implicated in the pathogenesis of CAD like serum iron levels (Reunanen et al., 1996). Iron plays an important role in production of free radicals and peroxidation of lipids, inflammation and myocardial ischemic damage (Neven et al., 2011). Steinberg showed that reduced iron played a role in the peroxidation of lipids (Steinberg, 1986). In a study, Ascheivo et al. found a relationship between iron consumption and infarction risk among the men whose diet did not include vitamin E (Ashehrio et al., 1993). Furthermore, Salonen et al. showed a two-fold increased risk of myocardial infarction in the subjects with above 200 g/l ferritin levels (Salonen et al., 1992). However, some studies have suggested that iron does not play a major role in development of CAD. More recent data from the National Health and Nutrition Examination Study (NHANES II) did not demonstrate a relationship between ferritin and cardiovascular mortality (Sempos et al., 2000). Magnusson and Pilote et al. did not find any association between serum ferritin and the risk of myocardial infarction (Magnusson et al., 1994; Pilote et al., 2000). In our study group high serum iron levels correlated with atherosclerosis and SS which show severity and complexity of disease.

Conclusions:
In conclusion, the findings of the present study showed elevated serum iron and CRP concentrations to be associated with increased syntax score and atherosclerosis severity.

Limitations:
Our study had some limitations; first of all, it was a retrospective study. Secondly, the patients, in whom history of coronary artery bypass graft surgery or percutaneous coronary intervention, were not included, which means that there was a potential bias in the selection of the study subjects.

References:


Table 1: Demographic, clinical, laboratory, and coronary angiographic characteristics of all patients, patients with no critical lesions and critical lesions with P value

<table>
<thead>
<tr>
<th></th>
<th>All patients (n:407)</th>
<th>No critical lesions (n:354)</th>
<th>Critical lesions (n:53)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age</td>
<td>56.4±10.7</td>
<td>55.6±10.6</td>
<td>61.3±10.1</td>
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<tr>
<td>Male-Gender n (%)</td>
<td>209 (51.4)</td>
<td>175 (20)</td>
<td>19 (27)</td>
<td>0.055</td>
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<tr>
<td>Diabetes</td>
<td>87 (21.4)</td>
<td>73 (48.4)</td>
<td>14 (37.8)</td>
<td>0.369</td>
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<tr>
<td>mellitus n (%)</td>
<td>162 (39.8)</td>
<td>136 (26)</td>
<td>26 (20)</td>
<td>0.175</td>
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<tr>
<td>Hypertension n (%)</td>
<td>148 (36.5)</td>
<td>123</td>
<td>25</td>
<td>0.197</td>
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<tr>
<td>Smoking n (%)</td>
<td>120±56</td>
<td>119±53.1</td>
<td>130±72.9</td>
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<tr>
<td>Glucose, mg/dl</td>
<td>0.9±1.7</td>
<td>0.9±1.8</td>
<td>0.8±0.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>127.9±56</td>
<td>126±57.6</td>
<td>136±45.7</td>
<td>0.27</td>
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<tr>
<td>LDL, mg/dl</td>
<td>170±116</td>
<td>168±118.2</td>
<td>178.4±103.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>0.75±1.8</td>
<td>0.5±0.93</td>
<td>2.4±4.09</td>
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<tr>
<td>C-Reactive protein, mg/dl</td>
<td>80.4±27.5</td>
<td>76.2±23.1</td>
<td>108.1±37.2</td>
<td>0</td>
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<tr>
<td>Syntax score</td>
<td>1.5±4.8</td>
<td>0</td>
<td>11.8±7.9</td>
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</table>

Table 2: Correlations between syntax score, C-Reactive protein and serum iron

<table>
<thead>
<tr>
<th>Syntax score</th>
<th>C-Reactive protein, mg/dl</th>
<th>Serum iron, mg/dl</th>
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<tr>
<td>Pearson Correlation</td>
<td>.261**</td>
<td>.380**</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>407</td>
<td>407</td>
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