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Original Article

Correlation of C-Reactive Protein and Serum Iron Levels with Syntax Score

Ozdemir, B.

Department of Cardiology Faculty of Medicine, Nigde Omer Halisdemir University, Campus, 51240, Nigde, Turkey

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Corresponding Author: betulozaltun@ohu.edu.tr

ABSTRACT

Cardiovascular disease is one of the most common causes of morbidity and mortality in the world. Atherosclerosis is an inflammatory process, and serum C-reactive protein (CRP) is an acute-phase protein rising in response to inflammation. Serum iron (Fe) is one of the essential metals for the human body. Inflammation and infection are characterized by changes in Fe metabolism. Since atherosclerosis is an inflammatory process, changes in CRP and serum Fe 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 the syntax score. This study included 407 patients with a mean age of 56.4±10.7 years. The majority of the patients were male (51.4%). In this study, 53 and 354 patients had critical and no critical lesions, respectively. According to the baseline coronary angiograms, the syntax score was calculated in all patients. The laboratory variables, including hemoglobin levels, blood glucose, creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, Fe, and CRP were also evaluated in this study. Regarding the laboratory parameters of all groups, the mean CRP levels, Fe levels, and syntax score were estimated at 0.75±1.8 mg/dl, 80.4±27.5 mg/dl, and 1.5±4.8, respectively. Furthermore, a high syntax score correlated with Fe and CRP levels. Based on the findings of the present study, elevated serum Fe and CRP concentrations were associated with increased syntax score and atherosclerosis severity.

Keywords: Atherosclerosis; C-reactive protein; Serum iron; Syntax score

Corrélation du Score Syntaxique avec les Taux de Protéine C-Réactive et de Fer Sérique

Résumé: les maladies cardiovasculaires sont l'une des causes les plus fréquentes de morbidité et de mortalité dans le monde. L'athérosclérose est un processus inflammatoire, et la protéine C-réactive (CRP) sérique est une protéine de phase aiguë qui augmente en réponse à l'inflammation. Le fer sérique (Fe) est l'un des métaux essentiels pour le corps humain. L'inflammation et l'infection sont caractérisées par des changements dans le métabolisme du Fe. L'athérosclérose étant un processus inflammatoire, des changements dans les taux de CRP et de fer sérique sont attendus. Cependant, la distribution de la maladie dans les artères coronaires est importante pour la mortalité et la morbidité. La distribution de la maladie peut être déterminée par le score syntaxique. Cette étude a inclus 407 patients avec un âge moyen de 56,4±10,7 ans. La majorité des patients étaient de sexe masculin (51,4%). Dans cette étude, 53 et 354 patients avaient respectivement des lésions critiques et des lésions non critiques. Selon les angiographies coronariennes de base, le score syntaxique a été calculé chez tous les patients. Les variables de laboratoire, y compris les taux d'hémoglobine, la glycémie, la créatinine, le cholestérol des lipoprotéines de basse densité, le cholestérol des lipoprotéines de haute densité et les triglycérides, Fe et CRP ont également été évalués dans cette étude. En ce qui concerne les paramètres de laboratoire de tous les groupes, les valeurs moyennes des niveaux de CRP Fe et du score syntaxique ont été estimées à 0.75±1.8mg/dl, 80.4±27.5mg/dl, 1.5±4.8 respectivement. De plus, des niveaux de score syntaxique élevés étaient corrélés avec les niveaux de Fe et de CRP. Les résultats de la présente étude ont montré l'association de concentrations élevées

de fer sérique et de CRP avec une augmentation du score syntaxique et de la gravité de l'athérosclérose.
Mots clés: Athérosclérose; Protéine C-réactive; Fer sérique; Score syntaxique

INTRODUCTION

Cardiovascular disease (CVD) is one of the most common causes of morbidity and mortality in the world. Moreover, this disease is epidemic at present, and it is the single most important disease worldwide 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 for cardiovascular diseases, such as hyperlipidemia, hypertension, cigarette smoking, obesity, diabetes mellitus, and a positive family history of cardiovascular disease. The majority of the risk factors can be eliminated by changing lifestyle or diet. Serum C-reactive protein (CRP), which is an established marker of systemic inflammation and an acute-phase protein of hepatic origin, rises in response to inflammation. The elevation of serum CRP level lacks specificity; however, as a biomarker, it has been implicated in a variety of illnesses, including rheumatoid arthritis, sepsis, and atherosclerosis more recently (Pepys et al., 1985). After an acute cardiac event, CRP remains elevated for several months. In the ECAT study, an increase in CRP was associated with an increase in cardiac events by 50%. The CRP, in conjunction with two other markers (i.e., N-terminal pro-brain natriuretic peptide and cystatin C) was shown to be a risk factor for cardiovascular and all-cause mortality (Zethelius et al., 2008). Atherosclerosis is a disease characterized by

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. A CRP level of ≥ 3 μg/mL in serum is used in the clinical setting as an unspecific marker for inflammation, infection, and tissue injury associated with an acute-phase response (Koenig, 2013). The CRP is considered a predictor of future cardiovascular events (Emerging Risk Factors et al., 2012). Atherosclerosis is a complex inflammatory pathological process initiated by lipid deposition in the arterial wall with the subsequent recruitment of circulating leukocytes. Moreover, the CRP contributes to endothelial dysfunction and hypertension by inhibiting nitric oxide (Verma et al., 2002), increasing endothelin-1 production, and impairing endothelial-dependent vascular relaxation (Guan et al., 2009). Serum iron (Fe) is one of the essential metals for the human body. On the one hand, this metal is essential to almost all organisms. On the other hand, it becomes toxic when accumulates above certain thresholds. The ability of Fe to stably interconvert between the most common oxidative forms ($Fe2^+$ and $Fe3^+$) favors its participation in Fenton reaction and the generation of highly reactive hydroxyl radicals. This subsequently damages DNAs, lipids, and proteins which cause cells to undergo Fe-mediated oxidative stress and programmed cell death. Therefore, it is necessary to maintain Fe homeostasis for correct cell functioning and Fe-mediated tissue damage prevention (Gozzelino and Arosio, 2016). Inflammation and infection are characterized by changes in Fe metabolism, involving 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 the Fe stored in the

human body might be positively correlated with the risk of coronary heart disease. According to this hypothesis, the production of free radicals that are subsequently modified to low-density lipoprotein cholesterol (LDL) is important in the development of atherosclerosis, and Fe may stimulate the catalysis of oxidation reactions that produce free radicals (Meyers, 1996; Sempos et al., 1996). Serum Fe levels are also correlated with inflammation, and it is well-known that atherosclerosis is an inflammatory process. The syntax score (SS) (Synergy of PCI with TAXUS and Cardiac Surgery), 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 (Valgimigli et al., 2007; Serruys et al., 2009a). Since CAD is an essential inflammatory disease, it is hypothesized that CRP and Fe levels could be associated with the complexity of CAD as assessed by SS. This study aimed to investigate the relationship of CRP with Fe levels and the severity of coronary atherosclerosis assessed by SS in patients with stable CAD.

MATERIAL AND METHODS

Study population. This study included 407 consecutive patients with stable angina pectoris 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. The study protocol that was in accordance with the Declaration of Helsinki was approved by the Ethics Committee of Adana Numune Training and Research Hospital, Adana, Turkey

Laboratory measurements. Blood samples were collected before the implementation of index coronary angiography after an overnight fast and analyzed in the laboratory of Adana Numune Training and Research Hospital, Adana, Turkey. The studied laboratory variables included hemoglobin levels, blood glucose, creatinine, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), Fe, and CRP. Normal ranges were 0.0-0.80 and 60-180 mg/dL for CRP and Fe, respectively.

Angiographic analysis. All patients underwent coronary angiography via the standard Judkins technique. Moreover, 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, the 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 the vessels of > 1.5 mm based on the SS calculator. Lesions over 70% were considered critical in this study.

Statistical analysis. The data were presented as mean±SD or median for quantitative variables and counts or percentages for categorical variables. Differences between the two groups were analyzed using a t-test or Mann-Whitney U test for continuous variables, as well as Chi-square or Fisher's exact tests for categorical variables. Furthermore, multivariate logistic regression (stepwise backward conditional analysis) was used to determine the independent predictors of the intermediate to high SS group using variables that were found to be significant in the univariate analysis ($P<0.05$). The data were analyzed in SPSS software (version 23.0, SPSS Inc., Chicago, Illinois)

RESULTS

This study included 407 patients with a mean age of 56.4±10.7 years. The majority of the patients were male (51.4%). The mean SS was obtained as 1.5±4.8 (range: 0.0-31). According to the results, 53 and 354 cases had

critical and no critical lesions, respectively. Table 1 tabulates the baseline characteristics of the patients. There was no significant difference between the groups in terms of diabetes mellitus and hypertension. Moreover, 73 and 14 patients in no critical and critical lesion groups had diabetes mellitus, respectively, which showed no significant difference between them in this regard. Similarly, no critical and critical lesion groups included 162 and 136 patients with hypertension, respectively, which revealed no significant difference. Regarding the laboratory parameters, glucose, creatine, LDL, triglyceride, CRP, and serum Fe levels were measured in this study. A significant difference was observed between the groups in terms of CRP and serum Fe. The groups also showed differences regarding the SS. Furthermore, SS was found to be correlated with CRP and serum Fe levels. In our study, high SS levels, as well as an increase in serum Fe and CRP levels, were remarkable (Table 2).

DISCUSSION

The CAD is a leading cause of mortality, morbidity, and disability. Moreover, it has been associated with several risk factors, including gender, age, elevated blood cholesterol, diabetes mellitus, cigarette smoking, hypertension, and atherosclerosis. In this study, a significant difference was found between patients with and without critical coronary lesions in terms of serum Fe and CRP levels. Furthermore, the results indicated that C-reactive protein and serum Fe levels were significantly associated with SS. The SS accounts for the number and location of the coronary lesions, thereby determining the myocardium under the risk of ischemia. Numerous syntax trials confirmed that SS was an independent predictor of short-and long-term morbidity and mortality, as well as adverse cardiovascular outcomes in a wide range of patients, including stable CAD (Serruys et al., 2009b; van Gaal et al., 2009; Garg et al., 2010). Inflammation plays an important role in all stages of atherosclerosis (Drakopoulou et al., 2009); accordingly, CRP and serum Fe are frequently used in clinical practice as the markers of inflammation. Serum CRP, an acute-phase protein from the liver, is elevated in response to inflammation and improves risk prediction for patients with CAD (Koenig, 2013). In addition, high CRP levels are 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. In the same vein, CRP has been shown to impair the endothelial progenitor cells and fibrinolysis, increase collagen degradation in monocytes, activate the complement system, and probably be involved in the uptake of LDL-C by macrophages, thereby turning them into foam cells (Jialal et al., 2004; Devaraj et al., 2009; Bisoendial et al., 2010). In the present study, the correlation of CRP levels and atherosclerosis with SS indicates an increase in the severity and complexity of coronary atherosclerosis in high CRP levels. Several trace elements have been also implicated in the pathogenesis of CAD, such as serum Fe levels (Reunanen et al., 1996). Iron plays an important role in the production of free radicals and peroxidation of lipids, inflammation, and myocardial ischemic damage (Neven et al., 2011). Steinberg (1986) showed that reduced Fe played a role in the peroxidation of lipids. In a study conducted by Ascherio et al. (1994), a relationship was found between Fe consumption and infarction risk among the males whose diet had no vitamin E. Furthermore, Salonen et al. (1992) showed a two-fold increase in the risk of myocardial infarction in the subjects with a ferritin level of > 200 g/l. However, some studies have suggested that Fe does not play a major role in the 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). Additionaly, Magnusson et al. (1994) (Pilote et al., 2000) revealed no association between serum ferritin and the risk of myocardial infarction. In our study, high serum Fe

levels correlated with atherosclerosis and SS, showing the severity and complexity of the disease.

Table 1. Demographic, clinical, laboratory, and coronary angiographic characteristics of all patients and those with no critical and critical lesions

	All patients (n=407)	No critical lesions (n=354)	Critical lesions (n=53)	P-value
Age	56.4±10.7	55.6±10.6	61.3±10.1	0
Male-Gender n (%)	209 (51.4)	175 (20)	19 (27)	0.055
Diabetesmellitus n (%)	87 (21.4)	73 (48.4)	14 (37.8)	0.369
Hypertension n (%)	162 (39.8)	136 (26)	26 (20)	0.175
Smoking n (%)	148 (36.5)	123	25	0.197
Glucose, mg/dl	120±56	119±53.1	130±72.9	0.2
Creatinine, mg/dl	0.9±1.7	0.9±1.8	0.8±0.1	0.65
LDL, mg/dl	127.9±56	126±57.6	136±45.7	0.27
Triglyceride, mg/dl	170±116	168±118.2	178.4±103.1	0.5
C-Reactive protein, mg/dl	0.75±1.8	0.5±0.93	2.4±4.09	0
Serum iron, mg/dl	80.4±27.5	76.2±23.1	108.1±37.2	0
Syntax score	1.5±4.8	0	11.8±7.9	0

Table 2. Correlation of syntax score with C-reactive protein and serum iron

		C-Reactive protein, mg/dl	Serum iron, mg/dl
Syntax score	Pearson Correlation	0.261**	0.380**
	Sig. (2-tailed)	0.000	0.000
	N	407	407

In conclusion, the findings of the present study showed the association of elevated serum Fe and CRP concentrations with increased SS and atherosclerosis severity.

Regarding the limitations, one can name the retrospective design of the present study. Moreover, the non-inclusion of the history of coronary artery bypass graft surgery or percutaneous coronary intervention of the patients may have posed potential biases in the sampling procedure.

Ethics

I hereby declare all ethical standards have been respected in preparation of the submitted article.

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