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Conditioned risk factors in patients with coronary heart disease

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Objective Coronary artery disease (CAD) risk factors are increasing in our country. The present study was performed to determine the prevalence of new (conditioned) risk factors among patients with CAD.
Methods In 85 patients with ischemic heart disease (IHD) we study the presence of risk factors including plasma fibrinogen, serum ferritin, serum iron and serum uric acid. The diagnosis of IHD in these patients depends on clinical history and examination, ECG, cardiac echo, and certain investigations including cardiac enzymes. Of these 85 patients, there are 23 females and 62 males, and also there were 50 persons selected as control group. We divided the patients into two groups: one group who had acute coronary heart disease (55 patients) and the second group with chronic IHD (30 patients).
Results The result of the study showed that there were statistically significant differences in the level of plasma fibrinogen between the two groups which were higher in the acute group, similar was the case with serum ferritin and serum iron but the level of serum uric acid was the same in both the groups.
Conclusion We conclude that plasma fibrinogen and serum ferritin can be used as a marker for the prediction of the presence of acute IHD.
Keywords ischemic heart disease , plasma fibrinogen, serum ferritin, uric acid

Introduction

Traditional cardiovascular disease (CVD) risk factors include dyslipidemia, elevated blood pressure, cigarette smoking and diabetes mellitus. Lifestyle factors are very important in the atherothrombotic disease process and therapeutic lifestyle changes – including a diet low in saturated fat, cholesterol and trans fats; regular physical activity; attainment and maintenance of a healthy body weight; and smoking cessation – remain central to preventive efforts.[1,2] Numerous novel and emerging risk factors are under study. Improved understanding of the roles of these factors in the atherothrombotic disease process may aid in risk stratification and/or in identifying and testing novel targets for therapy. Presently, the greatest utility of nontraditional risk factors such as inflammatory markers or measures of subclinical CVD are for identifying those individuals with at least moderate risk for a CVD event for whom aggressive therapy may be warranted.[3] Coronary atherosclerosis as a cause of coronary heart disease is more likely to develop with the presence of certain risk factors including elevated serum homocysteine; elevated serum triglyceride; elevated serum lipoprotein (a); elevated inflammatory markers e.g. CRP and elevated prothrombotic factors e.g. fibrinogen.[4]

Screening studies have shown that high blood pressure (BP), hyperlipidemia, smoking, family Hx and diabetes mellitus (DM) are predictive of less than half of all future cardiovascular events.[5] Also the predictive value of these traditional risk factors is limited among patients with premature atherosclerosis.

We have noticed that many patients with few traditional risk factors will develop an acute coronary syndrome (ACS) without prior symptoms of the disease. Many proteins, novel protein biomarkers, if externally validated may improve risk assessment for myocardial infarction (MI) and atherosclerotic CVD.[6,7] New risk factors have been identified which enhanced the risk for coronary artery disease (CAD), and these include: lipoprotein(a) [Lp(a)], homocysteine and fibrinogen, and these may be a marker in patients who may not have the conventional risk factors. Lp(a) is considered as a marker of thrombosis, although several prospective studies have found if any association between Lp(a) and CAD risk and cardiovascular risk tends to increase with Lp(a) value over 30 mg/dl.[8,9]

There is unclear mechanism of how it happens. Homocysteine promotes vascular diseases, but it may be related to deficiency of other factors including Vit. B_{12} and folates, especially among the elderly.[10]

Additional markers in patients with CAD, which is associated with adverse outcome includes infectious and inflammatory markers (CRP, TNF α, IL1, IL6) and infectious agents like CMV, Chlamydia, and *Helicobacter pylori*.[11–13] Fibrinogen is a large glycoprotein synthesised mostly in the liver. It is a clotting factor that activates thrombin, aggregates platelets, and stimulates smooth muscle proliferation. It is important in the development of premature atherosclerosis. Several studies have shown an impressive relation between plasma fibrinogen level and occurrence of CAD and stroke. Also fibrinogen level may be a risk factor for sequelae of CAD. Determinant of high fibrinogen level includes age, female sex, smoking, obesity, stress, use of oral pills, pregnancy, and consumption of large amount of dietary fat.[14]

Serum ferritin is positively correlated with serum CRP concentrations. Many solid conclusions come to the finding that serum ferritin is a positive acute phase reactant and is strongly associated with inflammatory processes including heart diseases and diabetes.

This role is thought to be due to prooxidant properties. In patients with serum ferritin concentrations >200 ng/mL, the risk of MI was 2.2 times greater than the patients with serum ferritin levels <200 ng/mL. This indicated that serum ferritin indirectly enhances the role of LDL-cholesterol in the induction of CVDs.[15–17]

Patients and Methods

We made a study on 85 patients with CHD for the presence of risk factors that include plasma fibrinogen, serum ferritin,

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serum iron and serum uric acid; and excluding patients with other traditional risk factors. We measured plasma fibrinogen, serum ferritin, serum iron and serum uric acid using BioFibri kit (Biolabo-SA, 02160, Maizy, France), Immunoassay kit (Biocheck, Inc., CA, USA; Catalog number: BC – 1025), Iron Ferrozine kit (Linear Chemicals, S.L., Barcelona, Spain) and Acid Eurique Enzymatique (Pap150; A u PAP 150 Kit; France), respectively. Twenty-three females, 62 males and 50 persons were chosen as control. The Dx. (diagnosis) of CAD was based on clinical history, ECG, certain laboratory investigations and cardiac echo. We divided the patients into two groups: one group with 55 patients who had acute CAD and another with 30 patients who had chronic CAD.

Statistical methods used include measurement of mean and standard deviation (SD), P value, and measurement of correlation coefficient between values.

Results and Discussion

The results of the study are shown in Tables 1–4.

The measurement of correlation coefficient values from Tables 1–4 shows that plasma fibrinogen level is significantly higher than control in patients with acute CAD and it is normal in those patients with chronic CAD, and the level of fibrinogen is higher in females. The results indicate that the association between high concentration of fibrinogen and risk of CVD is well established. The relation was first reported in preliminary results from the Northwick Park Heart Study in 1980.[18] The Prospective Cardiovascular Munster (PROCAM) study found that individuals who had low-density lipoprotein (LDL) and fibrinogen levels in the highest tertile had a 6.1-fold increase in coronary risk compared with those in the lowest tertile.[19]

Only 13 patients with acute CAD showed elevated level of serum ferritin and only 6 patients showed elevated level of serum iron which was statistically significant and there is positive correlation with plasma fibrinogen and most of these patients are males. Serum uric acid increased in 17 patients with acute CAD, but normal value in all patients with chronic CAD and there is a negative correlation with plasma fibrinogen. It was reported that 2.2 times greater levels of CVD were observed in the group with high serum iron (indicative of elevated serum ferritin) compared to the group with low serum iron. Serum ferritin was reported to be associated with CVD and cardiovascular mortality. Salonen et al. also reported that increase in serum ferritin accelerates the oxidation of LDL-cholesterol.[9,20]

In contrast to our study, it was reported in a prospective study performed in a French population; however, Galan et al. failed to find a positive association between serum ferritin and ischemic heart disease (IHD).[21] These findings matched well with the suggestions of Sempos et al.[22] 5 years earlier, as the results from the two studies did not support the hypothesis that positive body iron stores, as measured by serum ferritin, are associated with an increased risk of CVD, CHD or MI death. Dominguez-Rodriguez et al. suggested even more extreme findings that major adverse cardiovascular events is associated with lower serum ferritin levels in a study on a total of 196 and 30 days followed-up patients with a first non-ST elevation ACS.[23] Their observation was supported by an *in vitro* study that iron deficiency enhances atheroma inflammation through p38 mitogen activated protein kinase-nuclear factor-κB-extracellular matrix metalloproteinase inducer/matrix metalloproteinase-9 pathway.[24]

Serum uric acid had been shown mild elevation in about a quarter of patients with CAD. By contrast with

Table 1. **Mean plasma fibrinogen in CAD patients and control**

Group	Mean plasma fibrinogen in mg/dL	SD mg/dL	P value
Acute CAD	450	91.4 ±	0.002
Chronic CAD	365.5	59.2 ±	0.16
Control	306.3	58.8 ±	

CAD: coronary artery disease.

Table 2. **Mean of serum ferritin in CAD patients and control**

Group	Mean serum ferritin in ng/mL	SD ng/mL	P value
Acute CAD	126.6	121.3 ±	0.002 in male
Chronic CAD	48.3	39.7 ±	0.2
Control	49.2	39.9 ±	

CAD: coronary artery disease.

Table 3. **Mean of serum iron in CAD patients and control**

Group	Mean serum Fe in µmol/L	SD µmol/L	P value
Acute CAD	30	24.5 ±	0.02 in male
Chronic CAD	20.5	14.6 ±	0.26
Control	18.8	6.7 ±	

CAD: coronary artery disease.

Table 4. **Mean of serum uric acid in CAD patients and control**

Group	Mean serum uric acid in mg/dL	SD mg/dL	P value
Acute CAD	5.25	1.7 ±	0.02
Chronic CAD	3.75	1.02 ±	0.27
Control	3.58	1.02 ±	

CAD: coronary artery disease.

observational findings, there is no strong evidence for causal associations between uric acid and ischemic heart disease or blood pressure.[25] Kwada et al. recently overviewed and conducted meta-analysis on this association precisely, and concluded that hyperuricemia may increase the risk of IHD events, independently of traditional IHD risk factors.[26]

In conclusion, plasma fibrinogen, serum ferritin and to a lesser extent serum uric acid could be regarded as a marker and predictor of CAD and its sequelae. ■

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