Original Research Article

Role of high sensitive c-reactive protein and serum uric acid in coronary artery diseases: a case control study

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ABSTRACT

Background: Coronary artery diseases (CAD) are considered to be the major public health concerns throughout the world, including India. Despite significant improvement in the diagnosis, treatment and prevention, CAD remains the most common, acute, and chronic illness, which is the leading cause of mortality and morbidity in the world.

Methods: To estimate the serum uric acid and hs-CRP levels in coronary artery disease cases with diabetes mellitus and hypertension and compare with the healthy individuals.

Results: The mean serum uric acid levels were raised in cases (6.1±1.54 mg/dl) compared to the controls (5.16±1.007 mg/dl) which was significant statistically (p<0.008). The mean hs-CRP levels were raised in cases (7.1±8.122 mg/dl) compared to the controls (0.185±0.254 mg/dl) which was highly significant statistically.

Conclusions: Measurement of the levels of hs-CRP and serum uric acid in CAD might help in identifying the patient at increased risk of mortality.

Keywords: Coronary artery disease, Highly sensitive C - reactive protein, Serum uric acid

INTRODUCTION

Coronary artery disease is the most common, acute and chronic illness and is the leading cause of mortality and morbidity in the industrialized world. The cardiovascular epidemic is a worldwide phenomenon that accounts for almost 50% of all deaths in industrialized nations. In India 2.03 million deaths have occurred due to CAD by 2010 and prevalence of CAD is reported to be 2-3 times higher in urban population as compared to rural population, prevalence in urban 96.7% per 1000 population and 27.1% per 1000 population in rural.¹

Atherosclerosis the underlying cause of most CHD, is a process that starts early in life and progresses slowly and silently for decades. The clinical manifestations usually occur in the form of myocardial infarction, stroke, angina or sudden death.² Inflammation participates critically in atherosclerosis. Circulating levels of several inflammatory markers rise in individuals at risk for atherosclerotic events. In particular, elevation of plasma C-reactive protein (CRP), a nonspecific acute-phase reactant that is easily and reliably measured, has strong predictive power for cardiovascular events. Indeed, measurements of high-sensitivity CRP (hs-CRP) plasma levels add to both the prognostic information gleaned from assay of plasma lipid risk factors and the risk levels estimated by means of Framingham study–based criteria. Retrospective data suggest the hypothesis that hs-CRP plasma levels may be useful for guiding use of lipid-lowering therapy in individuals who appear to be at low risk according to traditional risk assessment. Increased concentrations of high-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, are associated with increased risk for coronary heart disease. Because of its relationship to inflammation, hs-CRP has considerable biologic variation. Thus, medical practitioners are ushering in an era in which...
the biology of inflammation in atherosclerosis will find its way into clinical application.

High-sensitivity C-reactive protein (hs-CRP) – is a quantitative analysis of very low levels of c-reactive protein, that may provide a novel method for detecting individuals at high risk of plaque rupture, as inflammation plays a major role in atherothrombosis. Cytokines, which cause the de novo hepatic production of acute phase reactants such as C-reactive protein, have been shown to increase in acute coronary syndromes even in the absence of myocardial necrosis. Therefore, CRP has been examined as a surrogate marker of other inflammatory mediators such as interleukin-6 and tumor necrosis factors-alpha to better understand the inflammatory component of atherosclerosis. Following a systematic review of the association between inflammatory markers and coronary heart diseases, the American Heart Association developed a scientific statement that recommends hs CRP as a sensitive assay for the prediction of vascular disease, compared to traditional assays for circulating C-reactive protein levels.

Uric acid is the product of purine metabolism, which is degraded in most mammals by the hepatic enzyme xanthine oxidase and is freely excreted in urine. Uric acid may also be used as an indicator of increased oxidative stress. The activity of xanthine oxidase increases during ischemia and intensifies during reperfusion in coronary endothelial cells. The base line increase in serum uric acid levels indicates coronary heart disease events. Each 50 micromol /L increase in the base line serum uric acid concentration was associated with 14% increase in cardiovascular mortality.

Aims and objectives

Aim and objectives were to estimate the levels of serum uric acid and hs CRP in coronary artery disease (CAD) cases with hypertension or DM. To see the association of serum uric acid and hs CRP levels in CAD cases with HTN or DM. To see the correlation of serum uric acid and hs CRP levels with CK MB in CAD.

METHODS

Study area

Ours is a hospital-based case control study. Study group and controls were selected from patients attending OPD and admitted cases at RL Jalappa Hospital and Research centre, Kolar and RL Jalappa Narayana Hruduyalaya Hospital, Kolar. Study group consisted sixty individuals in that thirty were diagnosed cases of coronary heart disease and thirty were healthy individuals as controls.

Sample collection

The inclusion criteria for case group were, 30 diagnosed cases of coronary artery diseases which include myocardial infarction, stable angina, and unstable angina of either gender, CHD cases with hypertension and diabetes mellitus, age above 18 years. The exclusion criteria were: acute infectious diseases, liver diseases, renal diseases, alcoholics and smokers.

The inclusion criteria for control group: Age and gender matched healthy population. The control group was screened for the complete blood tests and if they fall within normal reference range they were included as controls.

5 ml of blood was collected from the anti-cubital vein under complete aseptic precautions after obtaining informed consent from the case and control groups.

Informed consent

Institutional ethical committee clearance was taken before the start of the study. Informed consent was taken from all the subjects.

Parameters measured

In our study we estimated, blood glucose by Glucose Oxidase-Peroxidase method, CK-MB by Antibody kinetic method, Serum uric acid by Enzymatic colorimetric method and high sensitive C-reactive protein by immuno-turbidimetric method. Routine internal quality assurance confirmed and limitations of each parameter was considered.

Statistical analysis

The data collected was tabulated and statistical analysis was carried out using Statistical package for social sciences (SPSS) version 14.

Mean and standard deviation were calculated for serum uric acid, hs-CRP, random blood sugar, CK-MB individually for cases and controls and were compared using independent ‘t’ test.

Correlation between each parameter, i.e. correlation between CK-MB with hs-CRP and serum uric acid was done using Pearson’s correlation and p value of < 0.05 was taken statistically significant.

RESULTS

In our study, sixty subjects were selected considering the inclusion and exclusion criteria stated in the methodology. Among them 30 were CHD cases and 30 were age and gender matched controls.

The mean age of CHD in cases and controls were 52.6±12.5 and 46.4±15.84 respectively. The percentage of female in the cases and controls was 30% and the percentage of males in cases and controls was 70%. Table 1 depicts the independent t-tests comparing the mean values of the parameters between the cases and controls.
Figure 1: Independent t test for uric acid between cases and controls.

Figure 2: Independent t test for hs-CRP between cases and controls.

Figure 3: Independent t test for CK-MB between cases and controls.

Figure 4: Independent t test for RBS between cases and controls.

Figure 5: Correlation between serum uric acid and hs-CRP in cases.

DISCUSSION

The mean serum uric acid levels were raised in cases (6.1±1.54 mg/dl) compared to the controls (5.16±1.007 mg/dl) which was significant statistically (p<0.008). The mean hs-CRP levels were raised in cases (7.1±8.122 mg/dl) compared to the controls (0.185±0.254 mg/dl) which was highly significant statistically (p<0.001) as shown in figure 1, 2.

The mean CK-MB values were raised in cases (166.2667±100.37 u/l) compared to the controls.
The mean blood glucose levels were raised in cases (222.63±96.19 mg/dl) compared to the controls (87.36±8.70 mg/dl) which was highly significant statistically (p<0.001) (Figure 4).

**Correlation between CK-MB and hs-CRP in cases**

Pearson’s correlation, showed significant and positive correlation between serum uric acid and hs-CRP in cases (r= 0.479, p<0.007) as shown in Figure 5.

There was no significant correlation between CK-MB with hs-CRP and uric acid levels in cases.

In our case control study sixty subjects (n=60) were enrolled, of which 30 (n=30) were cases of coronary artery disease and 30 (n=30) were age and gender matched normal healthy controls. Baseline parameters such as random blood glucose, CK-MB were estimated in cases and controls.

Measurement of the serum levels of uric acid and high sensitive C-reactive protein in the cases was done and compared with the controls.

The levels of hs-CRP were found to be significantly increased in the cases when compared with the controls. This could be due to both atherogenic and thrombogenic vascular potential of hs-CRP and there is substantial evidence that hs-CRP might contribute directly to the pathogenesis of atherothrombosis.\(^7\)

Hs-CRP is a ligand binding protein that binds to the phospholipids of plasma membranes of damaged cells with subsequent limited activation of the complement system. This complement system enhances the damaged cells to express cytokines which stimulates the liver to release CRP at the inflammatory site in an autocatalytic manner. Hs-CRP was found to amplify the pro-inflammatory effects of several mediators which lead to promotion of development of atherosclerosis.

Hs-CRP is a potent stimulator of tissue factor production by macrophages in vitro. Tissue factor is the main initiator of coagulation and atherosclerosis in vivo and so its local concentration in the arterial wall is clearly related to coronary atherothrombotic events. Thus, the capacity of hs-CRP to enhance tissue factor production suggests a possible causative link between increased hs-CRP values and coronary events.

Kinji et al in 2006, have shown in their study that inflammation is closely related to insulin resistance and macro-angiopathy in type 2 DM and hs-CRP can be a useful marker for evaluation of pathophysiology in type 2 DM or vascular disease.\(^8\)

A pilot study was done by Sharma in 2008 on hs-CRP and oxidative stress in young CAD patients in India, and they observed that elevated hs-CRP along with dyslipidemia and oxidative stress added to the predictive value of premature CAD.\(^9\)

Soinio et al reviewed data from 1045 patients with type 2 diabetes aged 45 to 65 years, over a 7 year follow up period and it revealed that the mean hs-CRP levels were significantly higher in 157 patients who died from CAD and 254 patients who had a fatal or non-fatal CHD event.\(^10\)

De Beer et al measured CRP and creatinine kinase MB levels in patients with definite MI, patients with spontaneous or exercise induced angina, subjects undergoing coronary arteriography and patients with non-cardiac chest pain. They found that all individuals with infarction developed raised CRP levels and there was significant correlation between the peak CRP and CK-MB levels as seen in our study.\(^11\)

In our study, levels of serum uric acid were found to be significantly increased in cases when compared with controls. The increased uric acid levels in hypertensive cardiac diseases occurred may be due to the decrease in renal blood flow, which might have stimulate urate absorption.\(^12\)

Hypertension also results in microvascular disease and this can lead to local tissue ischemia and this in turn leading to increased uric acid synthesis. In ischemia, ATP is degraded to adenine and xanthine and there is also increased generation of xanthine oxidase. This increased availability of xanthine and xanthine oxidase results in increased uric acid generation as well as oxidant formation.\(^13\)

Hyperuricemia also has been shown to play a role in endothelial dysfunction, produced either directly by increased serum uric acid levels or through elevated xanthine oxidase activity. Other potential mechanisms by which hyperuricemia and elevated xanthine oxidase activity might produce vascular damage include increased platelet adhesiveness, smooth muscle proliferation and stimulation of inflammatory responses.\(^14\)

The first National Health and Nutrition Examination Study (NHANES I) done by Freedman and his co-workers demonstrated that each 60 μmol/L increase in uric acid level was associated with a 48% increase in risk for incident ischemic heart disease among women.\(^15\)

Fang and colleagues in the NHANES I epidemiologic follow up study done in United States in adults showed that increased levels of uric acid are related to increased cardiovascular mortality and morbidity.\(^16\)

Hamidreza et al suggested that asymptomatic hyperuricemia may be associated with the presence and
severity of angiographically-defined CAD in patients with suspicious symptoms for CAD.\(^\text{17}\)

There are few evidences showing that serum uric acid could possibly promote, rather than preventing oxygenation of low-density lipoprotein cholesterol and lipid peroxidation. This could lead to an increase in platelet adhesiveness, resulting in thrombus formation and can contribute to the development of atherosclerosis, increasing the likelihood of the developing cardiovascular disease.\(^\text{18}\)

High uric acid levels can also stimulate the release of free radicals, which might have been shown to be involved in adhesion molecule expression by inflammatory cells as well as inflammatory cell activation and adherence to the damaged endothelium.\(^\text{19}\) This ultimately results in endothelial injury, increasing the risk of cardiovascular disease development. This mechanism is supported by the study done by Levy et al in 39 male patients with chronic heart failure and 16 healthy controls, where they measured circulating uric acid and markers of inflammation, which showed a positive correlation between elevated UA levels and chronic inflammation in chronic heart failure.\(^\text{20}\)

A study by Kang et al in 2005, showed an elevation in plasma UA concentration is associated with an increased level of C-reactive protein that has been identified as an important indicator of myocardial infarction, stroke and vascular death as seen in our study.\(^\text{21}\)

**CONCLUSION**

The levels of highly sensitive C-reactive protein and uric acid were found to be higher in cases when compared to controls. High levels of hs-CRP may indicate coronary vascular inflammation state, which may be seen in patients with co-morbid conditions like hypertension, diabetes mellitus. Hyperuricemia may indicate endothelial dysfunction and oxidative stress which is commonly seen in CAD. Thus, the observation in the current data is that these abnormalities may contribute as a risk factor for mortality and morbidity seen in CAD patients. Hence, early assessment of hs-CRP and uric acid may help in decreasing the cardiovascular complications as their levels may serve as simple marker to identify patients at risk of mortality. They may also help in predicting the outcome and in effective management of these cases.

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