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Biochemical Causal-Effect of Circulatory Uric Acid, and HSCRP and their Diagnostic Correlation in Admitted Patients with Ischemic Heart Diseases

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ABSTRACT

Background and Objective: Ischemic heart disease (IHD) is one of the commonest reasons for morbidity and mortality universally. The principal etiopathology of IHD is coronary atherosclerosis. Serum uric acid (SUA), is found to be associated with IHD in several meta-analyses, independent of other risk factors. Hepatic acute phase reactant ''C-reactive protein (CRP)'' has a recognized contribution to vascular inflammation. Up till now, no sufficient data is yet available to show the correlation of both UA and HSCRP to each other and with IHD in our country. Therefore, this study was conducted to evaluate the causal-effect of SUA, and CRP and their diagnostic correlation in admitted patients with IHD.

Material and Methods: This was a case-control study, including 260 participants (160 patients with IHD and 100 healthy control). Blood samples were drawn from all participants within 24 hours of admission. Biochemical analyses included: fasting/random glucose, total lipid profile, creatinine, estimated GFR, SUA and HSCRP tests were completed for all participants were measured. According to their SUA levels participants divided into normourecemic and hyperuricemic groups (≤6.5 and > 6.5mg/dl sequentially). Likewise, serum levels of HSCRP into (< 3.5 mg/L and >3.5mg/L). A comparison of biochemical findings between IHD and controls were performed. SPSS-25 (IBM-USA) was applied for the statistical examination. Estimations of ORs, as well as 95% confidence intervals, where stated. P-values < 0.05 were allocated as significant. ROC-curve examination was analyzed to determine accuracy, specificity, sensitivity for both SUA and HSCRP mutually.

Results: The overall prevalence of hyperuricemia was 29% among all participants and was equivalent in both sexes, while HSCRP tertiles were higher significantly in males (p-0.003). Biochemical assays of SUA, HSCRP and lipid profile being higher in IHD patients significantly. There was a trend to have a higher risk of IHD occurrence in those with higher SUA and HSCRP mutually but not reach a statistical significance. After ROC-curve was analyzed, significant higher predictability of HSCRP vis SUA for diagnosing subjects with IHD as an outcome was reached. There was no strong association between the SUA and HSCRP. Still, the levels of HSCRP may have an association with increased SUA levels, but not reach statistical significance.

Conclusions: Serum levels of both UA and HSCRP increased significantly in patients with IHD. Higher levels of HSCRP could have an association with higher levels of SUA. Further studies are mandatory to complete our understanding pathophysiology of IHD and AS process.

Keywords: HSCRP, Ischemic heart diseases, hyperuricemia

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INTRODUCTION

Ischemic heart disease (IHD) is a chronic insidious disorder bearing grave morbidity and known to be one of the foremost identified reasons for mortality universally (1, 2). The principal etiopathology of IHD is a process of coronary atherosclerosis that involves buildup of atheromatic plaque, coronary arteries occlusion, afterward jeopardize blood flow (and hence, O2-supply) for the cardiac cells and ultimately their necrosis (3). There seems to be no compelling reason to argue the crucial rule of uric acid (UA) in cardiovascular disease (CVD). The 2018 expert agreement for the management of patients with hyperuricemia highpoints the significance of evaluating UA concentrations in those with hyperuricemia accompanied by high cardiovascular risk, although, the available data are still indefinite (4). Hyperuricemia showed substantial effects on IHD as an independent risk factor for mortality, where every 1 mg/dL increase in UA above normal was associated with 48% raised cardiovascular events (5).

The contributory role of vascular inflammation in the pathogenesis of AS is well established. As a "nonspecific acute-phase-polypeptide"; CRP synthesized by hepatic cells in response to inflammation could be measured as a general biomarker for IHD, therefore, serves as an independent marker for cardiovascular risk (6, 7). Beyond the skillful background of clinical trials, scarce data available on the burden, predictors, and results associated with highly sensitive-CRP (HSCRP) in "real-world" patients with IHD (8).

Up till now, no sufficient data is yet available to show the biochemical, clinical and diagnostic correlation of both UA and HSCRP with IHD in our country. Based on these conclusions, this work had been planned targeting assessment of such correlation.

MATERIALS AND METHODS

Study Design and Patients

This was a case-control study with 160 patients aged 60.9 (range 34-95) years and admitted in Shahidul-Mihrab cardiac center, Babylon; between January-August 2019. To ensure comprehensive data collection, those referred from other hospitals were excluded. Other exclusion criteria: those with any acute inflammatory disorder, malignancy, and renal impairment. All patients with IHD been diagnosed by cardiologists depending on history, clinical examination, ECG, echo findings, besides cardiac enzymes. The healthy controls (100 subjects) were selected from patients' attendants well matched for sex and age.

The study strategy adapted the ethical-guidelines of the "Helsinki-Declaration" as initiated by preceding approval from the ethical committee of the institution. The prerequisite of individual consent was obtained the entire work approved by the ethical committee of the University of Babylon.

Auxologic and Clinical Parameters

A thorough physical examination was performed for all participants, and data involving smoking, body mass index (BMI), age, hypertension, diabetes, and dyslipidemia were obtained from IHD patients archives.

Grouping and Definitions

The study subjects were divided (twice) into three and two groups according to the levels of HSCRP and UA. According to their UA levels, hyperuricemia was defined as UA levels > 6.5 mg/dl (so ≤ 6.5mg/dl considered as normourecemic); and further divided into tertiles [first: < 5 mg/dl, second: 5-6.5 mg/dl and the third tertile >6.5 mg/dl]. Similarly, subjects divided according to their HSCRP levels into two groups [≥ 3.5 mg/L and < 3.5mg/L based on study cutoff-point by ROC] and further divided again into three categories [< 1.0, 1.0-3.0 and > 3.0 mg/L (9).

Biochemical Measurements

Hematological samples were drawn from all participants within 24 hours of admission. Biochemical analyses included: fasting/random glucose, total lipid profile (triglycerides, total cholesterols, low/very-low-density lipoproteins, high-density lipoproteins), creatinine, and UA were evaluated utilizing the automated biochemical analyzer (Hitachi-HCP-7600, Japan). While serum HSCRP tests were completed by using the "CALBIOTECH® ELISA kit". White blood cell count of all participants was measured using available facilities of hospital' laboratories. THE estimated GFR was calculated for all participants.

Biostatistical Analyses

SPSS-25 (IBM-USA) was applied for the statistical examination. Continuous variables are displayed as mean± standard-deviation (or standard-errors). Contrasts amongst UA and HSCRP groups were performed with the "independent *t*-test" and ANOVA-analyses accordingly. Categorical parameters are stated as number/percentage. Estimations of ORs, as well as 95% confidence intervals, where stated. *P*-values < 0.05 were allocated as significant.

Predictive Model-Justification

Evaluation of cutoff-points, specificity, sensitivity, 95%-CI and area under the ROC-curve (AUC) was finalized to estimate the distinguishability of both UA and HSCRP biomarkers for diagnoses and prediction of IHD patients.

RESULTS

Basal Characteristics of the Patients

The main demographic features of study participants are exposed in table-1. There was no significant statistical variation between the IHD and control groups regarding the gender, R/FBS, BMI, creatinine, estimated GFR and WBC. Hypertension, diabetes mellitus, and smoking were significantly higher prevalence among IHD patients. The same can be observed regarding biochemical assays of SUA, HSCRP and lipid profile being higher in IHD patients significantly.

Table 1: Demographic characteristics of control and IHD patients.

	IHD Patients	Healthy Control	Significance
	Mean+/-Std. Error (min-max)	Mean+/-Std. Error(min-max)	
Age/years	60.9 (1.0) (34-95)	39.4 (1.1) (20-71)	< 0.05
Male No (%)	120 (59)	82 (41)	> 0.05
Female No (%)	40 (69)	18 (31)	> 0.05
Hypertension No (%)	82 (91)	8 (9)	< 0.05
DM No (%)	62 (91)	6 (9)	< 0.05
Smoking No (%)	76 (53)	68 (47)	< 0.05
R/FBS (mmol/dl)	9.6 (0.4) (4-25)	6.3 (0.9) (5.1-6.9)	> 0.05
White blood cells	10.34 (0.4) (4-25)	9.2 (0.1) (3-9.4)	> 0.05
BMI (kg/m^2)	27.4	27.0	> 0.05
HSCRP (mg/L)	8.59 (0.54) (1-51)	0.65 (0.14) (0.01-1.0)	< 0.05

Uric acid (mg/dl)	5.96 (0.14) (2.5-10.7)	4.4 (0.13) (1.9-0.13)	< 0.05
Creatinine (mg/l)	0.87±0.4	0.86±0.1 NS	NS
Estimated GFR (ml/min/1.73 m^2)	106.2±21.4	104.3±16.1	NS
Lipid profile (mg/dl)			
TG	2.7 (0.02) (2-3.4)	1.9 (0.06) (1.0-3.0)	< 0.05
TC	5.5 (0.05) (4.4-6.9)	3.9 (0.1) (2.0-5.0)	< 0.05
HDL	5.5 (0.5) (4.4-6.9)	3.7 (0.06) (2.0-5.1)	< 0.05
VLDL	0.54 (0.01) (0.2-0.9)	0.49 (0.01) (0.2-0.6)	> 0.05
LDL	4.3 (0.06) (2.6-5.7)	0.8 (0.07) (0.1-2.6)	< 0.05

DM: diabetes mellitus, R/FBS: random or fasting blood sugar, GFR: glomerular filtration rate, TG: triglycerides, TC: total cholesterol, HDL: high density lipoprotein, VLDL: very low-density lipoprotein, LDL: low density lipoprotein

Characteristics of the Patients according to Gender

Gender-related differences were given away through table-2. The prevalence of hyperuricemia was equivalent in both sexes. This is not the case for levels of HSCRP tertiles that were higher significantly in males (*p*-0.003).

Table 2: Gender Variations of Study Participants According to the Tertiles of Serum Uric Acid and Hypersensitive-CRP

	Serum Uric Acid Tertiles (mg/dl)				
	< 5.0	5.0-6.5	> 6.5	Total	
Female	18	8	32	58	> 0.05
Male	58	52	92	202	
Total	76	60	124	260	
	Serum Hypersensitive-CRP Tertiles (mg/dl)				
	< 1.0	1.0-3.0	> 3.0	Total	
Female	18	2	38	58	0.03
Male	88	10	104	202	
Total	106	12	142	260	

Characteristics of the Patients according to HSCRP and SUA

In this survey, the overall prevalence of hyperuricemia was 29% among all participants. Significant differences were detected between IHD the study groups considering both SUA and HSCRP tertiles (*p*-0.001) individually. There was a trend to have a higher risk of IHD occurrence in those with higher levels of SUA and HSCRP mutually but not reach a statistical significance; with ORs, *95% CI*, and significance: [0.71, 0.061-0.61 and 0.001] and [0.83, 0.64-1.07, and 0.006] chronologically (table-3).

Table 3: Comparison of Serum Uric Acid Tertiles between Ischemic heart Diseases Patients and Control Subjects

Uric Acid tertiles (mg/dl)	Total No (%)	IHD Cases		Healthy Control		*P-Value*	Odds Ratio	95% CI	*P-value*
		No (%)	Mean±SD	No (%)	Mean±SD				
< 5.0	124 (48)	58 (36)	5.96 ± 1.8	66 (66)	4.39 ± 1.3	0.001	0.71	0.06-0.61	0.001
5.0-6.5	60 (23)	36 (23)		24 (24)					
> 6.5	76 (29)	66 (41)		10 (10)					
Total No	260	160	Min-Max: 2.9-10.7	100	Min-Max: 1.9-7.3				
HSCRP tertiles (mg/L)									
< 1 (low risk)	99 (38)	7 (4.4)	8.59 ± 6.9	92	0.65 ± 0.4	0.001	0.83	0.64-	0.006

				(92)				1.07	
1-3 (normal)	16 (6.2)	12 (7.4)		4 (4)					
> 3 (high risk)	145 (55.8)	141 (88.2)		4 (4)					
Total No	260	160	Min-Max: 1.0-51.0	100	Min-Max: 0.01-1.0				

ROC curve models

To evaluate the discriminative capacity of both SUA and HSCRP for diagnosing IHD subjects, ROC-curves assays were applied. It revealed that for SUA, the AUC was 0.62 [*95% CI* 0.503–0.738] and *p*-0.2, while that of the HSCRP was 0.978 [*95% CI* 0.952–1.000] and *p*-0.000 consecutively. Henceforward, significantly higher predictability of HSCRP *vis* SUA for diagnosing subjects with IHD (figure-1).

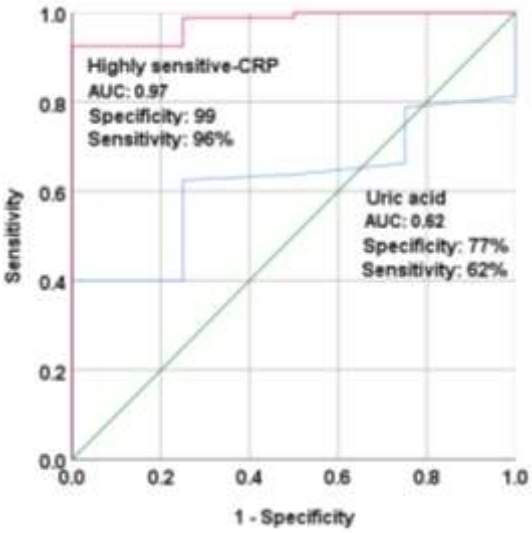

Figure 1: ROC curve for combined SUA and HSCRP

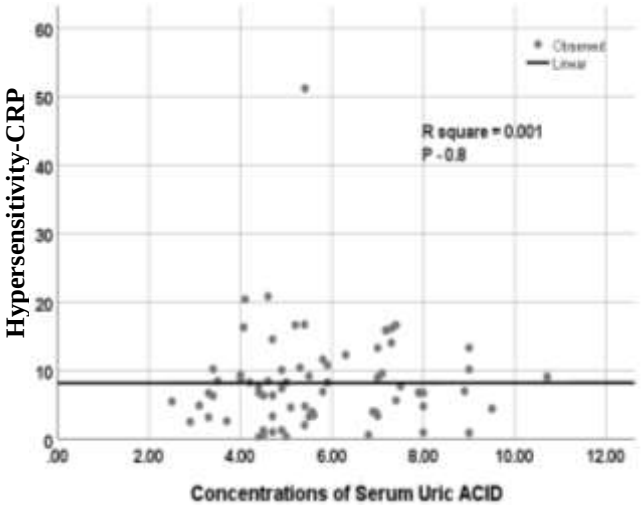

Figure 2: The scatter plots indicate a poor linear relationship between HSCRP and SUA

Correlation between SUA and HSCRP levels

To evaluate the strength of association of serum levels of UA to that of HSCRP in our participants, logistic regression analysis was completed twice: first, in all study applicants and second in IHD individually. In both situations, there were no strong associations among the two biomarkers (figure-2). Nevertheless, when we subdivided SUA into (hyperuricemic > 6.5 *vis* normourecemic $\leq$ 6.5 mg/dl) levels and HSCRP into (high HSCRP $\geq$ 3.5 *vis* Low HSCRP < 3.5 mg/L) on the base of the cutoff-points measured by ROC-models; and as the next statistical scatter plots showed; one can realize that levels of HSCRP weakly associate increases of SUA levels (figure-3).

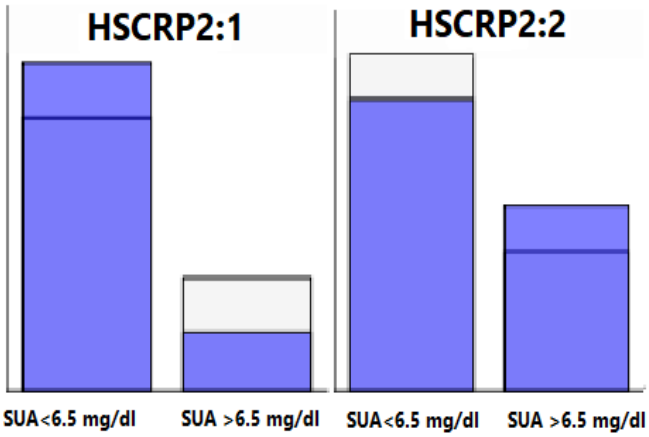

Figure 3: Statistical scatter plots subgrouping of two categories of serum HSCRP against two categories of serum uric. HSCRP 1= < 3.5mg/L and HSCRP 2=≥ 3.5 mg/L

DISCUSSION

The existing work verified that (1) the levels were significantly elevated in patients compared to control, and their blood values were an independent risk factor for IHD (though the results are not exposed). (2) the highness of SUA measures significantly in patients compared to control, however their blood values affected by adjusting other risk factors for IHD (3). There was a trend for HSCRP to increases with increasing SUA levels.

Risk factors of ischemic heart diseases

Our data appear to suggest that all studied risk factors (smoking, DM, and hypertension) were prevalent significantly higher among the IHD group, similar to numerous other studies (7, 10, 11). While BMI levels were comparable between the two study groups. Even though such variations did not have a great impact on the correlation among both SUA with HSCRP together or within the study groups, as multivariate regression analysis revealed (results not given away). Alterations in the serum lipids frequently noticed in IHD patients undeniably subsidize the development of AS. The results of this study revealed that the IHD group had higher values of lipid profile in comparison to healthy control. Several cohort scholars and experiments have uncovered the same association of lipid profile with an increased risk of IHD (12).

Serum uric acid and ischemic heart diseases

Our study revealed that SUA levels were parallel between sexes with an overall prevalence of 29%, and SUA significantly increased with higher ages of IHD patients. The view is very much consistent with Iraqi findings last year (10). In the interim, an overall incidence of hyperuricemia reported in the USA people was 21.4% (21.2% for men and 21.6% for women) based on "NHANES study" (13). An earlier large Chinese study displayed a higher frequency of hyperuricemia observed among male sex (14). Elucidations for these varying results were blurred, still, the high intra-individual gap in SUA levels that reaches variation amid people. Further clarification is the heterogeneity as regard to sample size among the studies.

As medical research has advanced, it has been determined that UA is not just a metabolite of nucleic acid but also strictly correlated to diseases like arterial-hypertension, DM, chronic nephropathy, and cardiometabolic syndrome (15). The relationship between SUA and IHD has been identified for more than five decades (16). A dual-pathways may be intricated; First: as a sequel of raised UA reabsorption/over-synthesis. Second: sequel of undue intake/breakdown of purine ancestors or increased activity of xanthine-reductase system (17). Many academics proposed that raised SUA independently associated with endothelial dysfunction in patients with IHD (18, 19). While others suggest that cardiocytes synthesize coronary-dilator adenosine following tissue hypoxia. Adenosine intern, degrading to UA by the vascular endothelium; in so doing, building up the UA with subsequent decreased intracellular PH with rapid UA outflux to the lumen (20). Worth mentioning, SUA may defend vascular damage arbitrated by oxidative-stress post-ischemia/reperfusion in rats (21). There is a rapidly growing literature that proposes that high oxidative-stressors closely associated with IHD as a body attempt to defend itself from the deleterious effects of free radicals by accumulating excess endogenous antioxidants, like UA. Remarkably, UA inhibits enzymatic endothelial dysfunction and conserves its capability to stimulate vasodilatation during oxidative stress (10).

Highly sensitive-CRP and ischemic heart diseases

I am not alone in my view that inflammation contributes to every phase of AS. As s proinflammatory protein HSCRP straightly contributes to the AS process (2, 7). Likewise, an increasing piece of evidence suggesting a strong predictive value of CRP in stable and unstable angina, independent of troponin and the burden of AS (22). Contrariwise, enhanced AS burden upraises HSCRP values. Even though more than few investigators believed that HSCRP denotes a biomarker of inflammation, but then again is not directly elaborated in the etiopathogenesis of AS (23). C-reactive protein deposited within the vascular-intima at the initial AS lesion causing chemotaxis of monocytes (11, 16). Razvan et al. and Grocer K. et al. reported that plasma HSCRP concentrations were not significantly associated with the severity of IHD (24, 25). Our study displays a strong correlation (with good discriminative capability by ROC) of HSCRP with IHD patients.

Correlation between SUA and HSCRP

Several researchers had proved a positive link between SUA and CRP levels in healthier and IHD patients (26). Contemporary revisions have publicized that high SUA levels correlate with "systemic-inflammation", raised CRP values, as well as dysfunctioning endothelium (27). Equally, another study detected an increase of SUA and HSCRP levels associated thoroughly with coronary-ectasia which is one variety of CAD (16). One potential explanation is that UA modifies the multiplication, movement, and NO-secretion of VSMC, facilitated by the expression of CRP (28). Other probable insight suggested that hyperuricemia could enhance the liver to express inflammatory particles through triggering of pro-inflammatory NF-κB signaling pathway (a principal mechanism) facilitating inflammatory reaction to different stimuli (29). To finish, HSCRP can attach lipoprotein, trigger the complement system, activate the access of the cells of inflammation besides other immune-regulatory actions, in that way, synthesize several inflammatory intermediaries, release O2-free radicals, and induce vessels injury and constriction, plaque synthesis, stenosed lumen, and the incidence of IHD (30). Uric acid has its precise imprint in some such way either affects or is affected in more than a few of these pathways. Still, numerous recent scholars report a weak or no significant association between SUA and HSCRP in patients with the acute coronary syndrome (2).

Even supposing, much of the contemporary arguments revolve about this opinion in many current meta-analyses, because of excessive discrepancies amongst studies that render it difficult to syndicate findings of all studies in one final strict conclusion. Therefore, considerable forthcoming

works are essential to elucidate the particular interrelationships between UA and HSCRP and to ascertain their definite contribution to IHD.

What Are the Clinical Implications?

- Our findings advocate that physicians have to monitor and pay attention to the serum levels of SUA in patients with IHD.
- Our findings classify patient groups who may get advantage from more dynamic risk-factors modulation, and to boost alteration of life-styles for the better outcome.

CONCLUSION

In conclusion, we observed that serum levels of both UA and HSCRP increased significantly in patients with IHD. It is recommended that cardiologists have to monitor the levels of these biomarkers during the management of patients with IHD. Higher levels of HSCRP could have an association with higher levels of the USA. High levels of SUA and HSCRP could be a cause or a consequence of IHD. These findings may be useful in understanding the mechanism and predicting the progression of patients with IHD and may contribute to the further prevention of the disease. Further studies are mandatory to complete our understanding pathophysiology of IHD and AS process.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests

LIMITATIONS OF THE STUDY

This study had a few limitations. First, given the high frequency of IHD, this is a single-center based practice and the number of studied patients was rather small. Therefore, we might have lost some factors. Second, patients with IHD are relatively varied concerning the presentation, thus far these patients were not evaluated discretely in this work. Third, the control group selected as age/sex-matched people free from any cardiac symptoms, we are unable to exclude with the inevitability that they may have asymptomatic IHD since coronary angiography has not been completed to the control group.

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