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A Comparative Study of Serum non-HDL Cholesterol, CRP and Uric Acid Levels in Metabolic Syndrome

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Original Research Article

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Abstract: The study aims to compare between serum non-HDL Cholesterol, CRP and Uric Acid Levels in Metabolic Syndrome. Fifty subjects of metabolic syndrome (MetS) (30 women, 20 men) who confirmed by the ATP III diagnosis criteria and have no any medical treatment were included in the study. Twenty healthy subjects constituted as the control group (13 women, 7 men). Blood samples were obtained after overnight fasting by using standard sampling procedure and measured fasting blood sugar, lipid profile, serum uric acid and CRP levels. Non–HDL-C was calculated by a formula (Non HDL-C = TC - HDL-C), C-reactive protein was measured using a commercially available ELISA Kit (Ray Biotech, Inc.) Uric acid level was determined using enzymatic (urease) method. Blood sugar and lipid profile were measured by using standard colorimetric commercial kit. Mean, Standard deviation and unpaired t- test (p value) were applied. A p value < 0.05 was considered as statistically significant. Anthropometric variables (blood pressure, BMI and WC) highly significantly ($p<0.0001$) increased except age ($p=0.37$ NS) in MetS (n=50) patients than control (n=30) groups. Lipid profile including TC, TG, LDL-C and VLDL-C showed statistically significantly raised ($p<0.0001$) whereas HDL-C observed decreased ($p<0.0001$) in same manners. In case N-HDL-C, CRP and serum uric acid levels were found statistical significantly elevated ($p<0.0001$) in MetS on comparison with control group. Non-HDL-C may be an independent risk factor for cardiovascular events in MetS. Monitoring HDL-C concentrations may reduce the cardiovascular risk. Therefore, non-HDL-C and CRP might be useful markers for predicting cardiovascular events in both high-risk and healthy individuals. Serum Uric Acid levels were significantly higher with MetS samples. Uric acid and non HDL cholesterol can be considered as a component of MetS.

Keywords: HDL- high density lipoprotein, CRP- C-reactive protein, MetS- metabolic syndrome.

INTRODUCTION

The metabolic syndrome (MS) is a growing general public health problem all around the world. Components of the MS including diabetes, hypertension, dyslipidemia, and obesity are closely associated with the risk factors defined for cardiovascular diseases, and it is known that each of these components has an atherogenic feature and increases the risk of coronary heart disease [1]. In 1999, the World Health Organization, proposed for the first time some diagnostic criteria for metabolic syndrome [33]. Afterward, the National Cholesterol Education Program´s Adult Treatment Panel III (NCEP/ATP III) [34] and the International Diabetes Federation (IDF) [35] updated both metabolic syndrome diagnosis and definition [2]. Five diagnostic criteria have been identified by the ATPIII, and the presence of any three features [central obesity, dyslipidemia (high triglycerides, low HDL), hypertension, and impaired fasting glucose (IFG)] is considered sufficient to diagnose the syndrome [3].

Current guidelines from the National Cholesterol Education Program (NCEP) rely on low-density lipoprotein cholesterol (LDL-C) as the primary therapeutic target in the prevention of cardiovascular disease (CVD) [4]. Emerging research has identified potential surrogate lipid markers for assessing cardiovascular risk, including apolipoprotein B (apoB), small dense LDL, LDL particle number, and non–high-density lipoprotein cholesterol (non–HDL-C).

Non–HDL-C is an established secondary target of therapy per the NCEP ATP III guidelines that remains underutilized in the clinical setting [5]. With conventional analysis, non–HDL-C is able to quantify total atherogenic burden by measuring the aggregate amount of "cholesterol" in all contributive particles. Non–HDL-C is a quick and simple calculation of TC minus HDL-C (TC - HDL-C), and can be obtained in the non-fasting state without affecting results.

Serum uric acid is a final enzymatic product of purine metabolism in humans, and it is suggested that hyperuricemia is associated with MetS, and they may have common pathophysiology [6]. In addition to MetS, elevated concentrations of uric acid are associated with a variety of cardiovascular conditions [7]. However, the association of uric acid and MetS remains controversial and limited experience exists on this relationship.

C-reactive protein (CRP) is a hepatic derived pentraxin that plays a key role in the innate immune response and is an independent risk factor for coronary artery disease (CAD) [8, 9]. Recent studies have found that CRP is an independent risk factor for CAD [8, 9]. High CRP levels have been related to the risk factors for dyslipidemia, hypertension, diabetes mellitus, and obesity [10]. CRP interacted multiplicatively with apolipoprotein B and other variables associated with metabolic syndrome [11].

In this study, we assessed and compare the levels of N-HDL, Serum uric acid and an indicator of inflammation as serum CRP in MS group patients. This low-grade inflammation, which has been used to estimate the risk for future cardiovascular events, could be thought to set up a link between the MS and atherosclerosis.

MATERIALS AND METHODS

The study was carried out in Clinical Biochemistry Department, Amaltas Institute of Medical Sciences, Dewas. Fifty subjects of metabolic syndrome (MetS) (30 women, 20 men) who confirmed by the ATP III diagnosis criteria and have no any medical treatment were included in the study. Twenty healthy subjects constituted as the control group (13 women, 7 men). Each patient provided informed consent for the study. Patients were excluded in the studies who were suffering from liver or renal dysfunction, acute or chronic inflammatory disease, malignancy, thyroid gland dysfunction, or current use of oral contraceptive.

Blood samples were obtained after overnight fasting by using standard sampling procedure and measured fasting blood sugar, lipid profile, serum uric acid and CRP levels. Non–HDL-C was calculated by a formula (Non HDL-C = TC - HDL-C), C-reactive protein was measured using a commercially available ELISA Kit (Ray Biotech, Inc.) Uric acid level was determined using enzymatic (urease) method. Blood sugar and lipid profile were measured by using standard colorimetric commercial kit.

The data was analyzed using MaxStat version 3.60 2015 software package. Mean, Standard deviation and unpaired t- test (p value) were applied. A p value < 0.05 was considered as statistically significant.

RESULTS

The present work is a hospital based cohort study included 50 subjects having metabolic syndrome, out of the 50 MetS with mean age of 38.76 ± 11.02 years, 30 were females and 20 were males with mean age 38.06±10.66 and 39.80±11.74 in the study group respectively.

Table-1: Comparison between all measured variables between MetS and control groups

S. No	Parameters	cases	Control	p-value
1.	Age (Years)	38.76±11.02	36.70±8.08	0.37 NS
2.	BPS (MM/Hg)	125.70±8.26	118.16±4.37	<0.0001 HS
3.	DPS (MM/Hg)	87.74±6.11	80.16±4.04	<0.0001 HS
4.	WC (Inches)	37.20±2.89	33.96±1.56	<0.0001 HS
5.	BMI (Kg/M^2)	26.37±1.48	23.08±1.12	<0.0001 HS
6.	FBS (Mg/dl)	147.04±23.61	90.29±7.39	<0.0001 HS
7.	TC (Mg/dl)	191.38±57.27	116.42±13.74	<0.0001 HS
8.	TG (Mg/dl)	185.50±44.48	102.57±10.14	<0.0001 HS
9.	HDL-C (Mg/dl)	28.40±5.62	47.90±5.22	<0.0001 HS
10.	LDL-C (Mg/dl)	125.88±57.07	48.00±14.97	<0.0001 HS
11.	VLDL-C (Mg/dl)	37.10±8.96	20.51±2.02	<0.0001 HS
12.	N-HDL-C (Mg/dl)	162.98±61.52	68.52±15.22	<0.0001 HS
13.	CRP (Mg/l)	3.73±1.37	0.90±0.33	<0.0001 HS
14.	UA (Mg/dl)	7.06±0.84	2.82±0.74	<0.0001 HS

All values are expressed in mean & standard deviation (Mean±SD). P values less than 0.05 indicates significant difference between the two groups or variables.

Abbreviation: NS= non-significant; S=significant; HS= highly significant BMI=body mass index; BPS=systolic blood pressure; DPS=diastolic blood pressure; WC= waist circumference; HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; TC=total cholesterol; TG=triglyceride; N-HDL-C= non high density lipoprotein cholesterol; CRP=C reactive protein; UA= uric acid.

In Table-1 shows, all anthropometric variables (blood pressure, BMI and WC) highly significantly ($p<0.0001$) increased except age ($p=0.37$ NS) in MetS (n=50) patients than control (n=30) groups. Lipid profile including TC, TG, LDL-C and VLDL-C showed statistically significantly raised ($p<0.0001$) whereas HDL-C observed decreased ($p<0.0001$) in same manners. In case N-HDL-C, CRP and serum uric acid levels were found statistical significantly elevated ($p<0.0001$) in MetS on comparison with control group.

Table-2: Comparison between all measured variables between male and female in Mets group

S. No	Parameters	Male	Female	p-value
1.	Age (Years)	39.80±11.74	38.06±10.66	0.591 NS
2.	BPS (MM/Hg)	125.75±7.48	125.66±8.88	0.912 NS
3.	DPS (MM/Hg)	86.75±5.44	88.40±6.53	0.355 NS
4.	WC (Inches)	35.55±1.84	38.30±2.96	0.0006 S
5.	BMI (Kg/M^2)	25.52±1.53	26.93±1.16	0.0005 S
6.	FBS (Mg/dl)	143.45±24.15	149.43±23.34	0.385 NS
7.	TC (Mg/dl)	187.65±71.30	193.86±46.39	0.711 NS
8.	TG (Mg/dl)	194.72±48.27	179.36±42.10	0.239 NS
9.	HDL-C (Mg/dl)	29.10±5.42	27.93±5.79	0.478 NS
10.	LDL-C (Mg/dl)	119.61±71.30	130.06±46.13	0.531 NS
11.	VLDL-C (Mg/dl)	38.94±9.65	35.87±8.42	0.239 NS
12.	N-HDL-C (Mg/dl)	158.55±76.01	165.93±50.87	0.682 NS
13.	CRP (Mg/l)	3.59±1.54	3.82±1.25	0.568 NS
14.	UA (Mg/dl)	7.47±0.77	6.79±0.79	0.0045 S

The abbreviation same as Table-1

There were not found much significant differences when compared between male and female in metabolic syndrome group. Only WC and BMI were significantly raised in female than male while serum uric acid was significantly higher in male than female of MetS group (Table-2).

DISCUSSION

Metabolic syndrome (MetS) comprises a constellation of CV risk factors that include abdominal obesity, insulin resistance, glucose intolerance, elevated blood pressure or antihypertensive drug treatment, low levels of high-density lipoprotein (HDL-C) cholesterol, and elevated triglyceride (TG) levels [12-14].

The demographic data including BMI, waist circumferences, and systolic and diastolic blood pressures were found to be significantly high in the patients with MS compared with the control group. It was similar to the Bahadir Kirilmaz *et al.*, who resulted in their study that demographic parameters were significantly raised in the metabolic syndrome patients [1].

In our work, FBS, lipid profile including total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides were found significantly increased whereas HDL cholesterol was found significantly decreased in cases compared to the controls. In agreement with the Marcin Gierach *et al*., [15] study who were found the lipid abnormalities probably have an important influence on the increase of CV risk. In patients with MetS, lipid metabolism disorders also have an unquestionable impact on the increase of the risk of CV death.

In another study concluded the statistically significant elevations in levels of total cholesterol, triglycerides, and LDL cholesterol and a significantly decreased level of HDL cholesterol were detected in the patients with the MS compared with the control group. This analysis was appropriate for dyslipidemia defined in the MS criteria [16].

In present study we found significantly elevated levels of non HDL cholesterol in metabolic syndrome patients on comparison with control group. The mechanisms linking non-HDL-C to MetS have not been completely explained though the following pathways have been proposed: low-grade inflammation, pro-coagulatory state, thrombosis, and atherosclerosis. Insulin resistance accompanied by obesity might also play a role through the development of impaired glucose tolerance and DM. Moreover, it is associated with a variety of CVD risk factors including hypertension, dyslipidemia, inflammation, endothelial dysfunction [17]. According to Saeed Ghodsi *et al*., [18] non–high-density lipoprotein cholesterol (Non-HDL-C) is known as a valuable predictor of premature atherosclerosis, coronary events like first Myocardial infarction and cardiovascular mortality. Another study performed a meta-analysis of the relationship between non-HDL-C reduction and CHD risk and showed that non-HDL-C is an important target of therapy for CHD prevention [19].

Liu *et al.*, [20] compared the diagnostic value of non-HDL-C as a prognostic factor of acute coronary events and myocardial infarction among healthy subjects and diabetics. Interestingly, in other studies, measured apoB and non HDL-C have been found to be highly correlated [21, 22]. Since neither TC nor HDL-C is significantly affected by food intake, non HDL-C can be measured not only in the fasting state but also in the post-prandial state. This high TG resulting in higher VLDL particles leads to high non HDL and Apo B levels. it has been suggested by Lopez VA *et al*., [23] that the considering the higher incidence of CVD in Indians, that the treatment has to be more aggressive and should begin at a lower threshold than is recommended for Western populations. The Third National Health and Nutrition Examination Survey (NHANES) linked mortality study performed by Chaoyang Li *et al*., analyzed data from 1,122 adults aged ≥ 20 years with diagnosed diabetes who participated in the survey. Those subjects with higher serum non HDL-C levels had a higher risk of death from total CVD. The authors concluded that, higher serum non-HDL-C concentrations were significantly associated with increased risk of death from CVD in diabetic patients [24].

High levels of CRP have been associated with increased risk of mortality due to myocardial infarction, stroke, peripheral arterial disease and ischemic heart disease in healthy men [25]. Circulating levels of several inflammatory biomarkers have been studied to assess their value in predicting CVD. The best characterized and well standardized biomarker of inflammation is C-reactive protein (CRP). In the present study CRP levels was found significantly higher in MS group than controls. Numerous studies [26] have now confirmed that CRP levels are elevated in patients with the MetS. Furthermore, it has been proposed that high sensitivity CRP (hsCRP) be added as a clinical criterion for MetS and for creation of an hsCRP-modified CHD risk score [27].

Arcari A *et al*., [28] found the elevated CRP levels have been associated with metabolic syndrome among European individuals. In a similar other finding for Taiwanese individuals, the study noted that CAD patients with metabolic syndrome had higher fasting serum CRP levels. CRP is an acute phase marker whose blood levels depend on interleukin-6 and other inflammatory proteins that stimulate its production by hepatocytes, lymphocytes, alveolar macrophages and monocyte-derived macrophages in atherosclerotic plaques [29].

It has been claimed that there is a chronic and low-degree inflammatory status in the MS. CRP indicates the existence and degree of inflammation involving the vascular endothelium. Elevation of CRP related with insulin resistance in MS has been shown in the Insulin Resistance (IRA) study by Festa and colleagues [30] Also, in the study of the Third National Health and Nutrition Examination Survey by Ford and colleagues, which included 8570 patients older than 20 years in which cases with the MS were compared with cases without syndrome, it was found that hs-CRP and fibrinogen levels and leukocyte counts were significantly high in patients with the MS [31].

Similarly Aswini Kumar and colleagues [32] study suggested that CRP (a marker of inflammation) level predicts the development of type 2 diabetes in metabolic syndrome. It has effect on atherothrombosis and acts as a useful risk marker for cardiovascular disease.

The uric acid levels were observed significantly higher in metabolic syndrome than control group. Uric acid has anti-oxidant effect, but it becomes a strong oxidant in the environment of metabolic syndrome. It stimulates vascular smooth muscle proliferation, induces endothelial dysfunction, decreased Nitric Oxide production, insulin resistance and causes TNF-alpha and CRP production [32]. Yuan *et al.*, [36] provide confirmation of in their findings on relationship between serum uric acid and metabolic syndrome, they have found significant positive linear relationship between serum uric acid levels and the risk of metabolic syndrome in a meta-analysis of prospective studies. Masuo *et al.*, [37] have demonstrated that serum uric acid concentrations predict subsequent weight gain. Sautin *et al.*, [38] suggest that hyperuricemia induces redox-dependent signaling and oxidative stress in adipocytes. Since oxidative stress in the adipose tissue has recently been recognized as a major cause of insulin resistance and cardiovascular disease, hyperuricemia-induced alterations in oxidative homeostasis in the adipose tissue might play an important role in these derangements [38]. In agreement with other authors [39, 40].

Uric acid and highly sensitive C reactive protein (hs-CRP) are risk factors associated with the metabolic syndrome. Treating higher Uric acid and hs-CRP can decrease the progression of metabolic syndrome [32]. Better and stricter life style changes and interventions can be implemented in those with higher uric acid and hs-CRP levels so that we can prevent complications of metabolic syndrome, specifically cardiovascular complications.

CONCLUSION

In our study concluded, non-HDL-C may be an independent risk factor for cardiovascular events in MetS. Monitoring HDL-C concentrations may reduce the cardiovascular risk. Therefore, non-HDL-C and

CRP might be useful markers for predicting cardiovascular events in both high-risk and healthy individuals. In is also showed that serum Uric Acid levels were significantly higher with MetS samples. Our findings propose that uric acid and non HDL cholesterol can be considered as a component of MetS. Regarding high prevalence of obesity and MetS as well as the potential link between hyperuricemia and CVD, future studies should be conducted to clarify the role of uric acid in the pathogenesis of Mets and the clinical significance of the current findings.

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