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Original Research Article

Concurrent Derangement of Lipid Profile and Risk Evaluation of Cardiovascular Diseases in Hyperuricemic Patients

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ABSTRACT

Background: The association of hyperuricemia and cardiovascular diseases is known for several years. However the exact role of uric acid in developing cardiovascular diseases is still not well established. Dyslipidemia is a well-known risk factor for development of cardiovascular diseases which often accompanies hyperuricemia.
Aim: aim of the study is to observe the association of dyslipidemia in hyperuricemic patients and to assess their risk of future cardiovascular diseases.
Materials and methods: The study is conducted retrospectively including 71 hyperuricemic patients and the data of lipid profile and its ratios were compared with 48 apparently healthy normouricemic controls.
Result: serum triglyceride (cases 179.732 ± 44.882, controls 167.937 ± 41.502), triglyceride/HDL ratio (cases 4.354 ±2.506; controls2.514±1.215), Total cholesterol/HDL ratio (cases 3.687± 1.066, controls 3.165±0.788), LDL/HDL ratio (cases 2.188 ± 0.811, controls; 1.835±0.708), were found to be elevated significantly in hyperuricemic patients. Total cholesterol, LDL was although higher in the patient group but was statistically non-significant. HDL cholesterol value in cases was lower as compared to the controls but was statistically not significant.
Conclusion: hyperuricemic patients are at a higher risk of developing future cardiovascular diseases not only because of hyperuricemia but also due to accompanying dyslipidemia. The frequent coexistence of dyslipidemia in hyperuricemic patients might have synergistic action along with uric acid in developing cardiovascular diseases in hyperuricemic patients. Follow up with lipid profile estimation and treatment with hypolipidemic drugs preferably targeting triglyceride may decrease the risk of cardiovascular diseases.

Key words: hyperuricemia, hypertriglyceridemia, dyslipidemia, cardiovascular diseases.

INTRODUCTION

Hyperuricemia can result from either due to overproduction, decreased excretion or both. [1] In general, hyperuricemia is defined as a plasma (or serum) urate concentration >405 µmol/L (>6.8 mg/dL). [1] Hyperuricemia can be classified as primary (innate) or secondary (acquired) depending upon the underlying etiology[1].An association of hyperuricemia with hypertension, diabetes, kidney disease, and cardiovascular disease has been observed since the late 19th century. [2,3] Previous studies have shown positive association of uric acid with hypertension, dyslipidemia and cardiovascular risk factors. [4,5] Since the level of uric acid, components of metabolic syndrome, dyslipidemia and cardiovascular risk factors all depend upon the lifestyle and food habit [6] that varies according to

regional variation and in different ethnic groups, the present study is aimed at evaluating the association of hyperuricemia and dyslipidemia (which is a well-known risk factors for cardiovascular diseases) in hyperuricemic populations attending a tertiary care hospital of Sikkim.

Uric acid is the end product of catabolism of the purine nucleosides adenosine and guanosine in human. The sources of purine may be either dietary or endogenous synthesis. Approximately 400mg of uric acid is synthesized daily within the body and another 300 mg is contributed from the dietary purine. [7] So the overproduction of uric acid may occur due to either over synthesis inside the body and also partly due to over intake.

Although the association of uric acid and cardiovascular diseases has been known for several years, controversy still exists whether uric acid is to be considered as an individual risk factor for cardiovascular diseases or it is just a coexisting marker. [3] Modernisation of lifestyle has increased the frequency of hyperuricemia in the general population. [6] When the level of uric acid exceeds 7mg/dl, supersaturation occurs and uric acid crystals start depositing over the vascular wall. [6] However, the value is even lower in women as compared to men. Monosodium urate binds with IgG of plasma. Monosodium urate-IgG complex is recognised by the Fc receptor of platelets and leads to activation of platelets. This process stimulates blood coagulation. There is release of cytokines and thrombi which progresses atherosclerosis. [6] Xanthine oxidase, a molybdenum- and iron-containing flavoprotein, oxidizes hypoxanthine to xanthine and then to uric acid. Molecular oxygen acts as oxidant in both the steps and gets reduced to hydrogen peroxide. In normal state, hydrogen peroxide is decomposed to H2O and O2 bycatalase. [8] Xanthine oxidase activity is increased in many conditions like myocardial infarction, reperfusion injury, heart failure and is associated with oxidative stress.

Dyslipidemia is a well-known factor for development of cardiovascular diseases. [9] One third of the total deaths occur due to cardiovascular diseases worldwide, two third of which occurs in developing countries like India. [9] Cardiovascular disease has become the leading cause of mortality in India. [10] Estimation of the lipid profile and the ratios of different lipid components is a useful tool for risk assessment of CVD. Several previous studies have documented the association of hyperuricemia and CVD. But the exact mechanism of action is still not well established. Since hyperuricemia is frequently accompanied with other risk factors for development of CVD like obesity, diet, dyslipidemia, hyperglycemia etc., it is still a matter of debate whether uric acid is just a coexisting marker or an individual risk factor for development of CVD.

Aim of the study: to observe the association of dyslipidemia as a risk factor for cardiovascular diseases in hyperuricemic patients.

Review of literature:

Several previous studies have observed the association of uric acid with CVDs. [3,11]

Meta-analysis done by Min Li et al and meta-analysis done by Seo Young Kim et al in their studies concluded that uric acid is a risk factor for development of coronary heart diseases. [12,13]

Tao-Chun Peng et al in their study on 14130 populations of US observed that serum LDL, TG, TC, apo B, TG/HDL ratio, apo B/ AI were associated significantly with serum uric acid whereas HDL cholesterol was associated inversely with serum uric acids. [14]

Sharma et al in their study observed significant positive correlation of serum TC, TG, LDL and significant inverse correlation of serum HDL with uric acid level in the hyperuricemic patients as compared to healthy controls. [15]

Sara Nejatinamini et al studied serum uric acid level in patients with metabolic syndrome and concluded that

patients with metabolic syndrome have higher uric acid level and uric acid might be an additional marker of metabolic syndrome. [16]

MATERIALS AND METHODS

The present study is a retrospective case control study including 71hyperuricemic cases with uric acid level more than 7mg/dl irrespective of the sex, with or without clinical presentation as gout and 48apparentlyhealthy normouricemic controls attending the outpatient department from January 2016 to November 2016.

Controls were selected from the patients who attended the outpatient department for pre-employment or post-employment general health check-up, who were apparently healthy without any specific health issue, with serum uric acid level < 5mg/dl, FBS <110 mg/dl and PPBS <140 mg/dl.

Duration of study: 11 months from January 2016 to November 2016.

The following biochemical data were collected for all the cases and controls from the departmental log book: serum uric acid, total cholesterol, triglyceride, HDL, and LDL.

Detailed clinical history including the past history was collected from the Medical Record Department of the Hospital. Statistical analysis of the data were carried out by unpaired students t-test using Microsoft excel software.

All the tests were performed in the autoanalyser EM 200 using documented standardised methods.

Inclusion criteria:

Hyperuricemic patients with serum uric acid level >7mg/dl with or without clinical manifestation of gout

Exclusion criteria:

1. Patients with frank diabetes mellitus.
2. Patients with very high GGT suggestive of alcohol dependence.

Test methods and principles used:

Serum uric acid: uric acid was estimated using uricase-peroxidase method.

Serum total cholesterol (TC): TC was performed by using CHOD-PAP method based on the formulation of Allain et al and the modification of Roeschlau with further improvements.

Triglyceride (TG): TG was performed by glycerol 3-phosphate oxidase (GPO) method.

LDL cholesterol: was performed by using LDL direct reagent based on modified polyvinyl sulfonic acid (PVS) and polyethylene-glycol methyl ether (PEGME) coupled classic precipitation method with the improvements in using optimised quantities of PVS/PEGME and selected detergents.

HDL cholesterol: HDL was estimated using HDL direct reagent based on modified polyvinyl sulfonic acid (PVS) and PEGME coupled classic precipitation method with the improvements in using optimised quantities of PVS/PEGME and selected detergents.

RESULTS

Table 1: comparison of lipid profile between the cases and controls

	Cases (mean±SD)	Controls (mean±SD)	*p* value
Uric acid mg/dl	8.562±1.480	4.170±0.572	<0.0001
TC mg/dl	179.732±44.882	167.937±41.502	0.1500
TGL mg/dl	205.084±95.509	130.25±56.250	<0.0001
HDL mg/dl	50.826±12.952	54.3±11.126	0.132
LDL mg/dl	105.393±33.237	98.073±32.201	0.2351
TG/HDL	4.354±2.506	2.514±1.215	<0.0001
TC/HDL	3.687±1.066	3.165±0.788	0.0045
LDL/HDL	2.188±0.811	1.835±0.708	0.016

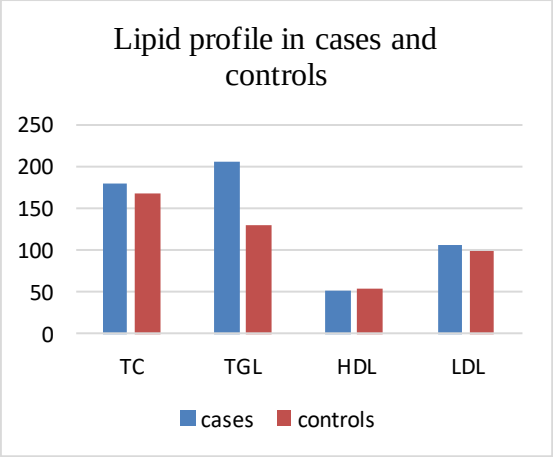

Figure 1: chart showing lipid profile in cases and controls.

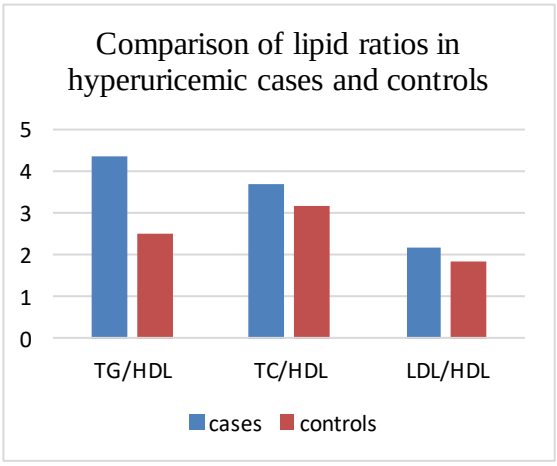

Figure 2: Chart showing comparison of lipid ratios in hyperuricemic cases and controls.

DISCUSSION

Comparison of lipid profile between hyperuricemic cases and controls:

From the table 1, it can be observed that the difference of triglyceride (TG), TG/HDL ratio, TC/HDL ratio and LDL/HDL ratio between the cases and controls were statistically significant with *p* values <0.0001, < 0.0001, 0.0045and 0.016 respectively.

The difference of total cholesterol, HDL and LDL did not become statistically significant.

Triglyceride: in the present study, serum triglycerides in hyperuricemic cases were very significantly elevated as compared to the controls.

Hypertriglyceridemia associated with hyperuricemic patients may be an additional factor leading to accelerated atherosclerosis and CVD in hyperuricemic patients. Several previous studies have observed association of hyperuricemia with cardiovascular diseases. [2,17,18]

Sharma and Sharma in their study found significant positive correlation of hypertriglyceridemia in hyperuricemic patients. [15]

According to some experimental studies, hypertriglyceridemia of very severe degree (4450mg/dl) cannot lead to atherosclerosis as the triglyceride rich lipoproteins are too large to enter into the arterial intima. However when the triglyceride value is raised mild or moderately (178-890), the triglyceride rich lipoprotein molecules are small enough to penetrate the vessel wall and can lead to atherogenesis. [19-22]

Triglyceride per se is not atherogenic but increased level of triglyceride rich lipoproteins (TRLs) such as VLDL, VLDL remnants, chylomicron remnants which are seen in hypertriglyceridemia are atherogenic. TRLs of both hepatic and intestinal origin takes cholesterol esters from HDL by the action of cholesterol ester transfer protein(CETP) and are hydrolysed by lipoprotein lipase(LPL) to form the remnants. The excess remnants that are formed in hypertriglyceridemia, due to delayed clearance gets build up in the plasma, accumulate in the endothelium and are engulfed by the macrophages to form foam cells which lead to formation of atherogenic plaque formation similar to LDL. [23,24]

Total cholesterol: total cholesterol in cases was although higher than the controls, but the difference did not attain any statistical significance.

Tao-Chun Peng et al, and Sharma et al in their studies observed positive correlation of total cholesterol with hyperuricemia. [14,15]

HDL cholesterol: in the present study, no statistically significant difference was observed between the cases and controls for HDL cholesterol.

Tao-Chun Peng et al, Sharma et al in their study observed inverse correlation of HDL cholesterol with hyperuricemia [14,15]

LDL cholesterol: in the present study, no statistically significant difference was observed between the cases as compared to controls for LDL cholesterol.

Tao-Chun Peng et al, Sharma et al in their study observed positive correlation of LDL cholesterol with hyperuricemia [14,15]

The difference of lifestyle, dietary habit, and racial variation can be the cause for the difference of observation with the present study.

TGL/HDL ratio: the present study showed statistically significant difference of

TG/HDL ratio in hyperuricemic cases as compared to controls with *p* value < 0.0001.
Tao-Chun Peng et al observed linear positive correlation of TG/HDL ratio in hyperuricemic patients. [14]
Protasio Lemos da Luz et al observed strongest association of TG/HDL ratio with the development of coronary diseases although some individual lipoproteins were also associated with the extent of coronary diseases. [25]
High TG/HDL ratio in the hyperuricemic population renders them at a higher risk of developing cardiovascular diseases.
Total cholesterol/HDL ratio: the TC/HDL ratio in cases was statistically significantly elevated as compared to the controls with *p* value 0.0045.
The ratio of TC/HDL is the best the predictor of ischemic heart diseases as observed by several prospective studies. [26]
LDL/HDL ratio: LDL/HDL ratios in cases as compared to the controls were statistically significant with *p* value 0.016.
Lipid ratios are better predictor for development of cardiovascular diseases as compared to the individual lipid components. [27]
LDL/HDL ratio has more predictive value for development of CVD in presence of hypertriglyceridemia. [27,28]

Juan Xu, Hao Peng et al in their study observed strongest correlation of serum triglyceride with serum uric acid. They also observed significant correlation of non HDL cholesterol and serum uric acid. [29]

Some of the previous studies observed that treatment of hypertriglyceridemia with fenofibrate or atorvastatin reduces serum uric acid level. [20,30,31]

Lowering of uric acid in experimental animals with allopurinol showed prophylactic prevention of fructose induced hyperuricemia and hypertriglyceridemia. [32] This suggests that hypertriglyceridemia and hyperuricemia occur due to a common mechanism and the same therapy can target both the conditions. [29]

Some of the previous prospective studies have observed that patients with high LDL/HDL ratio and associated hypertriglyceridemia as observed in the present study are at higher risk for development of cardiovascular diseases. [33,34]

From the present study it can be hypothesised that uric acid solely is not responsible for the development of cardiovascular diseases in hyperuricemic patients, but the associated dyslipidemia in the hyperuricemic people also exert synergistic action.

CONCLUSION

From the present study it can be concluded that the hyperuricemic patients are at a higher risk of developing cardiovascular diseases (CVDs) not only because of hyperuricemia but also due to the accompanying dyslipidemia in the form of hypertriglyceridemia, increased TG/HDL, TC/HDL & LDL/HDL ratio which are better predictive indicator for the development of future CVDs than the individual lipids. It can also be assumed that there is probably sharing of mechanism and/or confounding factors leading to hyperuricemia and dyslipidemia. Following up of the hyperuricemic people with estimation of lipid profile and use of hypolipidemic drugs targeting hypertriglyceridemia in these populations will definitely reduce the risk of development of future CVDs.

Limitations of the study:

Since the uppernormal limit of uric acid for women is lower than men, statistical analysis done separately for male and female would have conveyed more information on the pattern of dyslipidemia and risk of CVDs of male and female hyperuricemic people separately. The study being a retrospective one, some of the confounding factors like habit of alcohol consumption, smoking, physical activities etc. could not be considered in the present

study. A prospective cohort study and controlled clinical trial including larger study subjects and proper follow up will be able to provide more information on the development of CVDs in hyperuricemic people.

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