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Evaluation of relationship between hyperuricemia and hyperhomocysteinemia

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ABSTRACT

Aims: Hyperuricemia is generally a subclinical disorder. Uric acid takes part in the malignities, obesity-insulin resistance syndrome, and some other cardiovasculer problems. Plasma homocysteine (Hcy) levels are one of the major risk factors of coronary heart disease, one of the major reasons of adult mortality. In this study, it was aimed to determine relationship between hyperuricemia and hyperhomocysteinemia.

Methods: In this prospective research, 32 patients and 32 healthy controls were investigated. The age, sex, height, weight, complaints, medications and arterial blood pressure of the patients were measured and recorded. Moreover, whole blood test, fasting plasma glucose, serum lipids, sedimentation, cobalamin, folate, plasma total Hcy and uric acid levels were determined.

Results: In the patient group 62.51% was male and 37.5% was female. The mean age was 54.69+12.03. In the healthy controls 62.5% was male and 37.5% was female, and the mean age was 51.59+9.57. The difference between the mean ages of both groups was not significant ($p>0.05$). Uric acid levels were found to be 8.61±0.98 mg/dl in the patient group and 4.09±0.99 mg/dl in the control group, and this difference was significant ($p<0.001$). Hcy levels were found to be 10.99+1.42 µmol/L in the patient group and 6.67±0.80 gmoI/L in the control group. This difference was also statistically significant ($p<0.001$)

Conclusion: Hyperuricemia which is generally a subclinical disorder is accepted a coronary risk factor with the presence of other risks. Elevated plasma homocysteine is an independent risk factor for coronary heart disease. There are similar features of the both etiologia. Therefore we recommend to calculate the plasma homocysteine levels in hyperuricemic patients who have the risk of coronary heart disease and to treat the hyperuricemic patients having hyperhomocysteinemia and coronary risk factors.

Keywords: Malignity, uric acid, hyperuricemia, hyperhomocysteinemia

INTRODUCTION

Serum uric acid is the end product of purine metabolism. Protein intake in the diet affects serum uric acid concentration, since protein metabolism products are procurers in urate synthesis. Hyperuricemia, which can be seen significantly with hematological malignancies as well as solid tumors, can also be observed in other pathological conditions.[1,2] On the other hand, it has been stated in various studies that there is a relationship between hyperuricemia and coronary heart diseases. High serum uric acid levels increase platelet adhesion and adhesion, and circulating sodium urate microcrystals initiate events that will cause thrombosis. Also uric acid; plays a role in obesity-insulin resistance syndrome and mediates the atherogenic effect.[2-4]

The possibility of elevated serum uric acid to be associated with coronary heart disease. It has been shown that hyperuricemia increases when coexisting with other risk factors (hypertension, overweight, insulin resistance, hyperlipidemia and physical inactivity) in atherosclerotic heart diseases. The coexistence of these risk factors indicates that hyperuricemia may be a component of the insulin-resistance syndrome.[1-4]

Homocysteine (Hcy) is a sulfur-containing amino acid and is formed as a result of the demethylation of methionine. Methionine, an essential amino acid, is taken in the diet. Homocysteine is formed as an intermediate during the breakdown of methionine to cysteine by transsulfuration. The homocysteine formed is converted to cystathionine by cystathionine beta synthetase or to methionine by methionine synthetase. These enzymes use pyridoxal phosphate (B6), folate and cobalamin as cofactors.[5] Genetic defects of these enzymes, deficiency of vitamins lead to moderate or severe hyperhomocysteinemia. High plasma homocysteine levels are currently accepted as an independent risk factor for premature cardiovascular diseases and also a risk factor for thrombosis.[5]

An increase in plasma Hcy levels is observed in patients with folate and cobalamin deficiency. Total plasma Hcy is accepted as a valuable test in the diagnosis and follow-up of folate and cobalamin deficiency.[6] In some studies, it is accepted that Hcy is more sensitive than normal hematological tests in subclinical vitamin B12 and folate deficiency. 5-10% of patients with cobalamin deficiency have a clinical diagnosis of cobalamin deficiency, but have normal serum cobalamin levels. Plasma total Hcy levels were found to be more sensitive in determining cobalamin deficiency in these patients.[6]

In this study, we aimed to determine the plasma total Hcy levels in patients with hyperuricemia, to investigate whether there is a difference between these patients and those with normal uric acid values, and to investigate its relationship with cobalamin and folate.

METHODS

The study was carried out as thesis study in 1999. Institutional approval was obtained, ethics committee approval was not received at that time. All ethical procedures and standards were carried out in accordance with the 1975 Helsinki Declaration. This prospective research was accomplished by evaluating the clinical and laboratory results of 32 patients with hyperuricemia, 20 male and 12 female, and individuals with normal uric acid levels of 20 males and 12 females, followed in the Gülhane Military Medical Academy (GATA) Internal Medicine Clinic. Seven patients had gout. All patients were evaluated clinically and laboratory. The patients included in the study did not use any mineral and vitamin preparations for at least two months. Patients with renal dysfunction, malignancy, and patients using diuretics, especially in the thiazide group, were not included in the study because their uricemia-increasing effects were known. In all cases, the amount of purine in the diet was tried to be 800-1000 mg/day.

The age, sex, height, weight, complaints, medications and arterial blood pressure of the patients were measured and recorded. After 12 hours of fasting, whole blood test, fasting plasma glucose, serum lipids, sedimentation, cobalamin, folate and plasma total Hcy were determined from patients with elevated uric acid levels. Blood samples were taken into 10 cc plain blood and two 5 cc EDTA tubes, and their serum and plasma were separated. It was put in the -40°C degree freezer.

Hemoglobin, hematocrit and leukocyte determinations from the blood samples were performed on an automatic complete blood count device (CELL¬DYN 1600). Routine biochemical measurements were made in GATA Biochemistry Clinic, full-enzymatically, in a Technicon RA-1000 autoanalyzer. Serum B12 and folate measurements were made with a dual RIA kit in GATA Nuclear Medicine Clinic. Plasma total Hcy levels were measured by high pressure liquid chromatography (HPLC). Reference values for plasma total Hcy levels; 9.27-14.01 µmol/L for men and 7.67-11.3 µmol/L for women.

Statistical Analysis

Statistical calculations and graphics were made with SPSS statistical computer program (SPSS for windows 10.0) and Microsoft Excel program. In the statistical calculations of the values obtained between the groups, Student's t-test was used between the groups with normal distribution, Mann-Whitney U test, X2 test and correlation analysis were performed between groups that did not comply with the normal distribution.

RESULTS

The patient group includes 32 cases and the control group includes 32 cases. In the patient group 62.51% was male and 37.5% was female. The mean age was 54.69+12.03. In the healthy controls 62.5% was male and 37.5% was female, and the mean age was 51.59+9.57. The difference between the mean ages of both groups was not statistically significant (p>0.05).

Uric acid levels were found to be 8.61±0.98 mg/dl in the patient group and 4.09±0.99 mg/dl in the control group, and this difference was statistically significant (p<0.001). Hcy levels were found to be 10.99+1.42 µmol/L in the patient group and 6.67±0.80 gmoI/L in the control group. This difference was also statistically significant (p<0.001) (**Table 1**).

Table 1. Comparison between patients and healthy controls via laboratory and clinic

Parameters	Patient (n:32)	Control (n:32)	P
Folate (ng/ml)	11.55±4.47	13.75+2.87	p<0.05*
Vitamin B12 (pg/ml)	309.53±109.75	477.92±121.48	p<0.001*
Glycemia (mg/dl)	93.1±14.8	84.1±9.4	p<0.05*
Total cholesterol (mg/dl)	216.00±64.83	207.69±29.12	p>0.05
Urea (mg/dl)	37.44±11.63	34.81±6.64	p>0.05
Hemoglobin	13.9±1.5	13.5±0.8	p>0.05
Hematocrit	42.0±5.1	42.4±3.5	p>0.05
Body mass index (kg/m²)	25.81+2.84	26.66±3.24	p>0.05
Uric acid (mg/dI)	8.61±0.98	4.09±0,99	p<0.001*
Homocycteine (µmol/L)	10.99±1.42	6.67±0.80	p<0.001*
Trigliyceride (mg/dI)	209.06±168.67	144.91±51.87	p<0.05*
HDL cholesterol (mg/dI)	44.09±5.14	45.41±3.90	p>0.05
LDL cholesterol (mg1d1)	129.44±54.57	132.97:1-24.96	p>0.05
Creatinine (mg/dI)	1.02±0.2	0.86±0.2	p<0.005*
Sistolic blood pressure (mmHg)	136.25±17.83	118,59±7,95	p<0,001*
Diastolic blood pressure (mmHg)	86.09±9.13	75,62±7,16	p<0,001*
Age	54.69±12.03	51.59±9.57	p>0.05

Mean systolic and diastolic blood pressures were 136.25±17.83 and 86.09±9.13 mmHg in the patient group, and 118.59±7.95 and 75.62±7.16 mmHg in the control group, and the difference between them was statistically significant (p<0.001). However, there was no difference between those who were hyperuricemic and did not have any other disease.

When other risk factors of coronary artery disease (CHD) were analyzed, triglyceride levels were found to be 209.06±168.67 mg/dl in the patient group and 144.91±51.87 mg/dl in the control group, and the difference between them was significant (p<0.05). Cholesterol levels were found to be 216.00±64.83 mg/dl and 207.69±29.12 mg/dl, and the difference between them was not significant (p>0.05).

Serum LDL levels were 129.44±54.57 for the patient group and 132.97+24.96 mg/dl for the control group, there was no statistically significant difference (p>0.05). Serum HDL levels were 33.72±1.4 in the patient group and 39.34+1.3 mg/dl in the control group, which was not statistically significant (p>0.05).

Serum creatinine levels were measured as 1.02±0.2 mg/dI in the patient group. It was found to be 0.86±0.2 mg/dl

in the control group. This difference was also statistically significant (p<0.005) (**Table 2**). While serum urea level was 37.44±11.63 mg/dl in the patient group, it was 34.81±6.64 mg/dl in the control group, the difference between them was not significant (p>0.05) (**Table 1**).

Table 2. Correlation between serum uric asid levels and other parameters

	r	p
Homocycteine	0.863	p<0.001*
Folate	-0.295	p<0.05*
Vitamin B12	-0.499	p<0.001*
Trigliyceride	0.283	p<0.05*
Total cholesterol	0.108	p>0.05
LDL cholesterol	-0.026	p>0.05
HDL cholesterol	-0.182	p<0.05*
Glucose	0.320	p<0.05*
Urea	0.288	p<0.05*
Creatinine	0.380	p<0.005*
Sistolic blood pressure	0.490	p<0.001*
Diastolic blood pressure	0.542	p<0.001*
Hemoglobin	0.078	p>0.05
Hematocrit	0.110	p>0.05
Age	0.228	p>0.05
Body mass index	-0.086	p>0.05

Fasting plasma glucose levels, which were 93.1±14.8 mg/dl in the patient group and 84.1±9.4 mg/dI in the control group, were also statistically significantly different (p<0.05). The patient and control groups were compared in terms of folate and Vitamin B12 levels, which are directly related to Hcy metabolism. The difference between the two groups was statistically significant in terms of folate level (11.55±4.47 and 13.75±2.87, p<0.05, respectively) and Vitamin B12 level (309.53±109.75 and 477.92±121.48, p<0.001, respectively) (**Table 1**). There was no difference between the two groups in terms of body mass index (BMI). (25.81±2.84 and 26.66±3.24 kg/m2, p>0.05, respectively) (**Table 1**). There was no difference in terms of hemoglobin and hematocrit levels (13.9±1.5, 42.0±5.1 and 13.5±0.8, 42.4±3.5 and p>0.05).

Table 3. Correlation between homocystein and other parameters

	r	p
Uric acid	0.863	p<0.001*
Folate	-0.365	p<0.005*
Vitamin B12	-0.552	p<0.001*
Triglyceride	0.315	p<0.05*
Total cholesterol	0.066	p>0.05*
LDL cholesterol	-0.084	p>0.05*
HDL cholesterol	-0.297	p<0.05*
Glucose	0.327	p<0.005*
Urea	0.863	p>0.05
Creatinine	0.414	p<0.005*
Sistolic blood pressure	0.516	p<0.001*
Diastolic blood pressure	0.538	p<0.001*
Hemoglobin	0.158	p>0.05
Hematocrit	0.014	p>0.05
Age	0.153	p>0.05
Body mass index	-0.115	p>0.05

In the correlation analysis performed to investigate the relationship between serum uric acid values and plasma total Hcy levels, a strong correlation was found (r=0.863 p<0.001). According to this result, plasma total Hcy levels increase with the increase in serum uric acid. While there was a negative correlation between serum uric acid levels and folate levels (r=-0.295 p<0.05), a strong negative correlation was found between serum uric acid levels and Vitamin B12 levels (r=-0.499 p<0.001). In addition, a positive correlation was found between serum uric acid levels and serum triglyceride levels (r=0.283 p<0.05), while a negative correlation was found between serum uric acid levels and HDL levels (r=-0.182 p<0.05), cholesterol The correlation between and LDL was not statistically significant (r=0.108 p>0.05 and r=-0.026 p>0.05).

A positive correlation was also found between serum uric acid values and glycemia (r=0.320 p<0.05), urea (r=0.288 p<0.05), and creatinine (r=0.380 p<0.005). There was also a positive correlation between the increase in uric acid and blood pressure (r=0.490 p<0.001). There was no statistically significant correlation between serum uric acid and age and BMI (r=0.228 p>0.05 and r=-0.086 p>0.05). A negative correlation was found between plasma total Hcy and folate (r=-0.365 p<0.005) and a strong negative correlation with Vitamin B12 (r=-0.552 p<0.001). Again, a positive correlation was found with the triglyceride level (r=0.315 p< 0.05). A negative correlation was also found between plasma total Hcy levels and HDL (r=-0.297 p<0.05).

A positive correlation was also found between plasma total Hcy values and glycemia (r=0.327 p<0.005) and creatinine (r=0.414 p<0.005). There was also a positive correlation between plasma total Hcy increase and blood pressures (r=0.516 p<0.001). There was no statistically significant correlation between plasma total Hcy and age and BMI (r=0.228 p>0.05 and r=-0.086 p>0.05). The correlation between plasma total Hcy and hemoglobin and hematocrit were not statistically significant (r=0.228 p>0.05 and r=-0.086 p>0.05).

DISCUSSSION

Serum uric acid is the major end product of purine metabolism. Purine nucleotides are formed in the human body in three ways: by diet, by de novo biosynthesis (recycle) and by degradation of tissue nucleic acids. Therefore, hyperuricemia is seen together with abnormal cell turnover (myeloproliferative diseases, chemotherapy of malignant diseases). Serum uric acid level is mainly dependent on urinary excretion (glomerular filtration function and tubular reabsorption rate). Serum uric acid may increase in kidney diseases.[1,7] This situation is affected by physiological, metabolic events and various drugs.[7]

Dietary protein intake affects serum uric acid concentration, since protein metabolism products are the precursors of urate synthesis.[8] Various studies have reported that there is a relationship between hyperuricemia and coronary heart diseases. In the Honolulu study, Carlos et al.[9] found an association between high serum uric acid and coronary heart disease. However, it has not debated whether uric acid alone is an independent risk factor for coronary heart disease.

High serum uric acid levels increase platelet adhesion and adhesion, and circulating sodium urate microcrystals initiate events that will cause thrombosis. Uric acid plays a role in obesity-insulin resistance syndrome and mediates the atherogenic effect.[10] The direct etiological role of uric acid in atherosclerosis has been investigated and it has been stated that it can provide potent water-soluble natural antioxidant defense against damaging radicals.[10]

The possibility of elevated serum uric acid to be associated with coronary heart disease; It has been shown to increase when coexisting with other risk factors such as hypertension, overweight, insulin resistance, fatty liver, chronic inflammatory diseases, hyperlipidemia and physical inactivity in atherosclerotic heart diseases.[11-13] The coexistence of these risk factors indicates that hyperuricemia may be a component of the insulin-resistance syndrome.[9]

Clinical studies in hyperuricemic patients with coronary sclerosis show that uric acid clearance is decreased and the urate-creatinine clearance ratio is also decreased. Decreased renal clearance of urate is due to nephrosclerosis with advanced atherosclerosis.[9,10] Especially in CHD, which is one of the major causes of mortality in adults, an important development in recent years is increased plasma Hcy levels, which has entered the etiology as a major risk factor.[14,15]

Hcy is a sulfur-containing amino acid and is formed as a result of demethylation of dietary methionine in the body. The homocysteine formed is metabolized in two ways. It is converted to methionine by the enzyme methionine synthetase, and to cysteine by cystathionine beta synthetase. These enzymes use vitamins such as B6, B12 and folate as cofactors. Since homocysteine cannot be metabolized in the deficiencies of these enzymes, its plasma levels increase.[14,15]

It has been stated in many studies that the increase in plasma Hcy concentrations may be caused by both genetic defects of enzymes involved in metabolism and deficiencies of vitamins B6, B12 and folate due to drugs and nutrition.[16] In most of the studies conducted in recent years, it is accepted that high plasma Hcy concentrations may be a risk factor for cardiovascular heart diseases.[14-16]

There is a linear relationship between plasma Hcy concentrations and not only CAD, but also cerebral, carotid, peripheral artery lesions and venous thrombosis.[17] There are studies showing that the normal values of Hcy determined by gender, between 1.2 and 1.8 times the upper limit, at most 2 times increased, constitute a risk factor especially for CAD, higher values are associated with genetic hyperhomocysteinemia and these patients are more prone to venous and cerebral thromboembolism.[17]

Hofmann et al.[18] found high plasma Hcy concentrations in 35 of the patients with Type I diabetes mellitus in their study. They found Hcy levels to be higher especially in patients who developed micro and macrovascular complications. They emphasized that folic acid treatment would be beneficial in such patients.[18]

In this current study, whether there is a relationship between hyperuricemia, which is accepted as a coronary risk factor, and hyperhomocysteinemia. We compared the groups of 32 patients and 32 control cases with similar age and gender characteristics. We found the serum uric acid levels to be significantly higher in the patient group ($p<0.001$). We found the plasma total Hcy levels to be significantly higher in the patient group ($p<0.001$). A strong correlation was found in the correlation analysis performed to investigate the relationship between serum uric acid levels and plasma total Hcy levels. ($r=0.863$ $p<0.001$). According to this result, plasma total Hcy levels increase with the increase in serum uric acid.

It has been reported in previous studies that plasma Hcy levels have a strong negative correlation with serum concentrations of B6, B12 and folate, and this relationship is more significant with folate in young patients and vitamin B12 in elderly patients.[14,15] In our study, when we compared the patient and control groups, we found that vitamin B12 and folate levels were significantly different, but less in the patient group ($p<0.05$). When we compared the groups with normal and high Hcy levels in the hyperuricemia group, we found a negative correlation between both folate and vitamin B12 and Hcy. In our study, we also compared the previously determined risk factors for CAD in the patient and control groups.

In this study, although there was no alcohol intake, a positive correlation was found between serum uric acid levels and serum triglyceride levels ($r=0.283$ $p<0.05$). A negative correlation was found between serum uric acid levels and HDL levels ($r=-0.182$ $p<0.05$). 0.05), the correlation between cholesterol and LDL was not statistically significant ($r=0.108$ $p>0.05$ and $r=-0.026$ $p>0.05$). In short, these findings were all compatible with our hypothesis.

There are some limitations are existing in this current study. First of all, study population is small. Secondly, this is a single centered study. However, prospective nature of this research and favorable findings renders our results acceptable.

CONCLUSION

Hyperuricemia is generally asymptomatic and is considered a risk factor for coronary heart disease when evaluated together with other factors. Increased Hcy concentrations are also recognized as an independent risk factor for cardiovascular heart disease. Since both have similar etiologies, we think that if there is a risk of coronary heart disease in hyperuricemic patients, plasma Hcy concentrations should be measured, and hyperuricemia treatment should be performed in those with high levels.

However, although hyperuricemia and hyperhomocysteinemia are accepted as risk factors for cardiovascular heart disease, we do not know how there is a direct relationship between them, and we believe that additional studies should be done on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out as thesis study in 1999.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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