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HYPERURICEMIA – A WARNING SIGNAL FOR PREDIABETES?

D.LAKSHMI LALITHA*[1], B.SREEHARI BABU [2] , DSSK RAJU [3]

[1]Professor , Department of Biochemistry, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram-535217
[2,3] Assistant Professor , Department of Biochemistry, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram-535217

ABSTRACT

With an objective to study the effect of high uric acid levels on insulin resistance, *a total of 100 subjects were categorized into two groups (Group A and Group B) based on their serum uric acid levels*. They were investigated for fasting plasma glucose, insulin and HbA1c. HOMA-IR was calculated basing on plasma glucose and insulin. Fasting plasma glucose, insulin and HbA1c levels showed an increase in Group B subjects when compared to Group A. HOMA –IR which is the indicator for insulin resistance also showed an increase in Group B subjects when compared to Group A. This increase is statistically significant ($p<0.001$). The beneficial effect of uric acid as an antioxidant is challenged by its abnormal concentration in the serum. This may lead to prediabetes which, over a period of time, might progress to frank diabetes. Thus serum uric acid level can act as a warning signal for future onset of diabetes.

KEY WORDS: *eNOS, HOMA-IR, prediabetes*

D.LAKSHMI LALITHA*

Professor, Department of Biochemistry, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram-535217

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INTRODUCTION

Uric acid is an important metabolic end product that is formed from purine metabolism. Besides showing antioxidant property, uric acid may also be associated with higher plasma insulin levels which may be a feature of insulin resistance especially in cases where the uric acid levels are above the normal values. Pre-diabetes occurs when blood sugar levels are consistently higher than normal, but don't yet reach the level at which it may be diagnosed as diabetes. This condition is also named as impaired glucose tolerance. Normal blood level of uric acid ranges from 2.5- 5.6 mg/dl in females and 3.1-7.0 mg/dl in males[1]. Several epidemiologic studies have reported that high serum levels of uric acid are strongly associated with prevalent health conditions such as obesity, metabolic syndrome, diabetes, essential hypertension and renal disease.[2,3,4]The effect of hyperuricemia on the occurrence of prediabetes due to insulin resistance and subsequent development of diabetes has not been totally assessed by any study until now. The aim of the study is to observe the relationship between the uric acid levels in serum and insulin resistance in otherwise normal individuals.

MATERIALS AND METHODS

This is a case control study conducted in the Department of Biochemistry, MIMS, Vizianagaram. Subjects were selected from both outpatient and inpatient departments of MIMS hospital randomly during the period from January 2016 to November 2016. Written informed consent was obtained from all the participants and the study was approved by the institutional medical ethics committee. Demographic characteristics (name, age, sex), history of risk factors (family history, alcohol intake, smoking, medications etc), systolic and diastolic blood pressures, weight, waist hip ratio were recorded for all the subjects. All the subjects chosen had similar food habits and normal blood pressure levels. The subjects with waist hip ratio less than 0.8 only were included in the study.

Inclusion criteria

Fifty apparently healthy subjects of both the sexes between the age group of 40-60 years with serum uric acid levels below 6.3 mg/dl (which is the mean of the normal upper limit of both male and female values), were included under Group A. Equal number of healthy males and females between 40-60 years of age with serum uric acid levels above 6.3 mg/dl served as Group B.

Exclusion Criteria

1. Established cases of Diabetes and Hypertension
2. Obesity
3. Alcoholism
4. Smoking
5. Drugs causing uric acid excretion like NSAIDS, losartan, fenofibrate etc and those causing decreased uric acid excretion like diuretics, pyrazinamide etc
6. Diseases like psoriasis and leukemias which influence serum uric acid levels.

Total 5 ml of venous blood sample was drawn from each participant after overnight fast of 8-10 hours. 2 ml of blood was collected in fluoride vial and 3 ml blood was taken in plain vial. Serum and plasma were separated for the estimation of glucose, insulin, HbA1c and uric acid. Plasma glucose was estimated by glucose oxidase peroxidase end point method. [5-,7] serum uric acid was estimated by modified Trinder end point method.[8-10] HBA1c was estimated by ion exchange resin method [11-13] and insulin was estimated by CLIA. HOMA –IR was calculated basing on plasma glucose and serum insulin levels using the formula, fasting glucose concentration (mg/dl) times fasting insulin concentration (IU/ml) divided by 405.[14]

STATISTICAL ANALYSIS

Data was expressed as Mean and Standard deviation (mean ±SD). Statistical significance between Group A and Group B observed, the Z test was performed using Microsoft Excel and SPSS software 16.0.The statistical significance was determined at 5% ($p < 0.05$) level.

RESULTS AND DISCUSSION

Table I
(A) & (B) Comparison of demographic features in both the groups

Table I (A)

Age (years)			
S No	Study groups	Range	Mean±SD
1	Group A (n=50)	40 - 60	50.1±5.7
2	Group B (n=50)	41 - 60	51.48±5.39

The above table shows mean age in both the groups.

Table I (B)

Sex distribution in both study groups			
S No	Study groups	Male	Female
1	Group A (n=50)	30 (60%)	20 (40%)
2	Group B (n=50)	28 (56%)	22(44%)

The above table shows percentage sex distribution in both the groups

Table II
Comparison of serum uric acid between both the groups

Serum uric acid (mg/dl)			
S No	Study groups	Range	Mean ±SD
1	Group A (n=50)	3.7 - 6.1	4.75 ±0.65
2	Group B (n=50)	6.7 - 8.9	7.39±0.45

p<0.001

Table II shows that there is an increase in serum uric acid in Group B when compared to Group A. It is statistically significant (p<0.001). This may be a consequence of excessive production of uric acid or inefficient excretion from the body or in rare cases, both together.[15]

Table III
Comparison of fasting plasma glucose in both the groups

Fasting plasma glucose (mg/dl)			
S No	Study groups	Range	Mean ±SD
1	Group A (n=50)	65 --98	80.74 ±7.30
2	Group B (n=50)	101-124	116.04 ±5.93

p<0.001

Table III shows that there is increase in fasting plasma glucose in Group B when compared to Group A. It is statistically significant (p<0.001).

Table IV
Comparison of HbA1c in both the groups

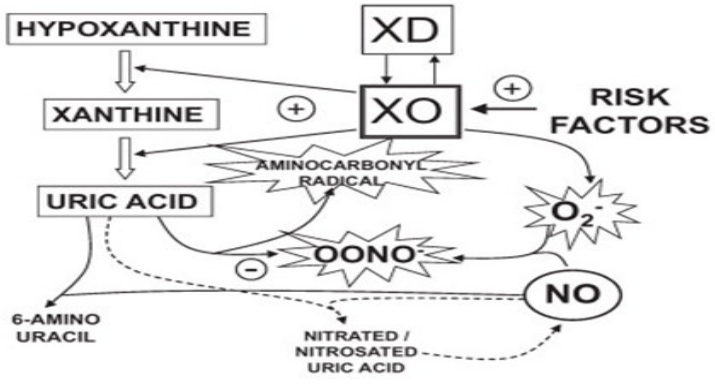
HbA1c (%)			
S No	Study groups	Range	Mean ±SD
1	Group A (n=50)	3.8 - 5.6	4.59 ±0.48
2	Group B (n=50)	4.3 - 6.8	5.5 ±0.53

p<0.001

Table IV shows that there is increase of HbA1c in Group B when compared to Group A. It is statistically significant (p<0.001).

Uric acid, at physiological concentration, has antioxidant effect and thus acts as an endothelial protective factor. However, when uric acid production is in excess involving xanthine oxidase, it paradoxically, plays a prooxidant role as the reactive oxygen species (ROS) and hydrogen peroxide are also produced in excess. These cause the formation of peroxy nitrite when reacting with endothelial nitric oxide. Nitric oxide is also utilized for the formation of nitrated or nitrosated uric acid and 6-amino uracil, thus reducing the bioavailability of nitric oxide (Fig 1). [16-18]

Figure 1
Prooxidant role of Uric acid



The above figure depicts the role of uric acid in decreasing the bioavailability of nitric oxide by forming peroxy nitrite, nitrated/nitro sated uric acid and 6-amino uracil.[18]

Nitric oxide (NO) is formed from arginine by nitric oxide synthase (NOS). The enzyme is a dioxygenase utilizing NADPH and molecular oxygen. Endothelial nitric oxide (eNOS) is seen in endothelial cells, platelets, endocardium and myocardium to produce NO and facilitate arterial relaxation. It is inactivated due to the strong and direct interaction with caveolin-1[17,] Calmodulin is required to modulate its activity. The binding of calcium-activated calmodulin to eNOS displaces caveolin-1 and activates eNOS. Hyperuricemia also inhibits nitric oxide bioavailability by reducing the interaction between eNOS and calmodulin. [19,-21]However, Insulin requires nitric oxide to stimulate glucose uptake and therefore non availability of nitric oxide causes a rise in the plasma glucose level. [22]

Table V
Comparison of fasting plasma insulin in both the groups

Fasting plasma insulin (mIU/L)			
S No	Study groups	Range	Mean ±SD
1	Group A (n=50)	10 - 18	14.44±2.49
2	Group B (n=50)	23 - 38	29.18±3.45

p<0.001

Table V shows that fasting plasma insulin is observed to be higher in Group B when compared to Group A. It is statistically significant (p<0.001).

Table VI
Comparison of HOMA-IR in both groups

HOMA-IR			
S No	Study groups	Range	Mean ±SD
1	Group A (n=50)	1.9 - 3.71	2.86 ±0.49
2	Group B (n=50)	6.48– 10.76	8.40 ±1.09

p<0.001

Table VI shows that there is increase of HOMA-IR in Group B when compared to Group A. It is statistically significant (p<0.001).

Hyperuricemia inhibits phospho-Akt (Ser473) response to insulin and increased phosphor-IRS1 (Ser307) in liver, muscle and fat tissues [23], thus directly inhibiting insulin signaling and causing insulin resistance.Insulin stimulates urate anion exchanger and/or the sodium-dependent anion cotransporter in renal proximal convoluted tubule facilitating urate reabsorption.Higher insulin levels are known to reduce renal excretion of urate [24] causing hyperuricemia. Insulin resistance can impair glycolytic pathway. This causes diversion of glucose towards HMP shunt through glucose 6 phosphate which in turn enhances purine biosynthesis and consequently, an excessive production of uric acid

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CONCLUSION

The beneficial effect of uric acid as an antioxidant is challenged by its presence in abnormal amount in the serum. Hyperuricemia contributes for hyperinsulinemia which in turn causes decreased excretion of uric acid. These lead to prediabetes which, over a period of time, might progress to frank diabetes. Thus serum uric acid level can act as a warning signal for future onset of diabetes.

CONFLICT OF INTEREST

Conflict of interest declared none.

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Reviewers of this article

Dr. N. Lakshmana Kumar

Professor and Head, Biochemistry, GSL Medical College , NH 16 , Lakshmipuram , Rajanagaram , Rajamahendravaram , Andrapradesh 533296.

G. Bakhya Shree M.S. (Research)

Coordinator and Trainer, Department of Biotechnology and Life Sciences, Dexter Academy, Madurai, Tamilnadu

Prof.Dr.K.Suriaprabha

Asst. Editor , International Journal of Pharma and Bio sciences.

Prof.P.Muthuprasanna

Managing Editor , International Journal of Pharma and Bio sciences.

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