Hyperuricemia is a risk factor for cardiovascular risk?

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Received: 25 December 2018
Accepted: 30 March 2019

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ABSTRACT

Background: Uric acid is the end product of purine metabolism in humans degraded by the hepatic enzyme, urate oxidase (uricase), to allantoin, which is freely excreted in the urine. However, during the Miocene epoch (20 to 5 million years ago), 2 parallel but distinct mutations occurred in early hominoids that rendered the uricase gene non-functional. Uric acid (UA) is a known endogenous scavenger, which provides a major part of the antioxidant capacity against oxidative and radical injury.

Methods: The present study was conducted over a period of one year on outpatients attending the General Medicine Department at Narayana General Hospital, Nellore. The study was included 998 subjects (500 male and 498 female) and authors excluded other complications. Data were analyzed by SPSS software.

Results: Serum uric acid of the subjects were measured. The mean and standard deviation were calculated for all the Biochemical parameter. The significance between the groups was determined using Student t-test for equality of means. The two-tailed P value is less than 0.0001, which is statistically significant. Confidence interval: the hypothetical mean is 1.0000 and the actual mean is 6.4600. The difference between these two values is 5.4600. The 95% confidence interval of this difference from 5.3489 to 5.5711. Intermediate values used in calculations; t = 96.4583, df = 999 and standard error of difference p = 0.057.

Conclusions: About 53% of the subjects of the study are hyperuricemia, with about 74% of these subjects (or about 39% of the total) diagnosed with hypertension or diabetes mellitus or both, indicating a high CVD risk.

Keywords: Antioxidant, Cardiovascular disease, Hyperuricemia, Uric acid

INTRODUCTION

Uric acid is the end product of purine metabolism in humans degraded by the hepatic enzyme, urate oxidase (uricase), to allantoin, which is freely excreted in the urine. However, during the Miocene epoch (20 to 5 million years ago), 2 parallel but distinct mutations occurred in early hominoids that rendered the uricase gene non-functional. Uric acid (UA) is a known endogenous scavenger, which provides a major part of the antioxidant capacity against oxidative and radical injury.¹

However, at high levels, uric acid can shift from an antioxidant to a pro-oxidant factor (shuttle capacity), depending on the characteristic of the surrounding microenvironment (e.g., uric acid levels, acidity, depletion of other antioxidants, reduced nitric oxide,
availability). Accordingly, high UA values have been associated with metabolic syndrome, hypertension and cardiovascular disease (CVD). There have been many studies in the last few years particularly on the relationship between hyperuricemia and hypertension. The question of whether hyperuricemia is the cause or the effect of hypertension has not been emphatically answered. The preclinical studies of Mazalli et al, however, appear to indicate so. Hyperuricemia is also known to be the intermediary in the fructose-induced metabolic syndrome. Recent studies point to the association between hyperuricemia, hypertension and diabetes mellitus (DM). Nakagawa et al, proposed that hyperuricemia has a role in the development stage of insulin resistance. However, hyperuricemia is less important after the development of insulin resistance as well as obesity. The studies of Han et al, indicate that hyperuricemia precedes insulin resistance. Their studies also show that peripheral insulin resistance plays a more important role in the development of hypertension than hepatic insulin resistance. They concluded that peripheral IR is a reasonable therapeutic target when hypertension is induced by hyperuricemia.

Cui LF et al, very recently studied the relationship between serum uric acid levels and hypertension in healthy Chinese cohorts of different ages. Their results show that a positive relationship exists between serum uric acid levels and hypertension only in the age group of 41-50 years. Kuwabara M et al, studied the risk of hypertension and diabetes mellitus in metabolically healthy individuals. Their results show that obesity increases the risk of diabetes even when the fasting blood glucose is normal. Further, hyperuricemia becomes an independent risk factor for developing hypertension in lean individuals without DM. They showed that a 1 mg/dl increase in serum uric acid (SUA) increases the risk of diabetes and hypertension by 27% and 19% respectively. Thus, the body of literature clearly establishes the complex interplay between hyperuricemia, hypertension and insulin resistance, as well as cardiovascular disease (CVD).

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion. A reduction in glomerular filtration rate (GFR) increases serum uric acid, although a significant compensatory increase in gastrointestinal excretion occurs.

Hyperuricemia also may result from increased net tubular absorption. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by a urate/anion exchanger and a voltage sensitive urate channel. Organic anions such as lactate decrease urate secretion by competing for urate through the organic anion transporter, whereas several substances, including probenecid and benziodarone, have opposite effects. Hyperuricemia is usually defined as 6.5 or 7.0mg/dL in men and 6.0 mg/dL in women.

Increased in uric acid could be a mechanism to maintain blood pressure and erect position in case of very low salt ingestion, so to benefit neuronal development and function. The development of modern, industrial societies characterized by extreme behavioral modifications (sedentary lifestyle and unlimited food supply) has occurred in a time period too short to allow genomic and metabolic adaptation. The uricase loss may represent a potential risk for health, as the prevalence of hyperuricemia is increasing in India and Asian countries, as well as in developing countries characterized by dietary and lifestyle changes.

METHODS

The present study was conducted over a period of one year on outpatients attending the General Medicine Department at Narayana General Hospital, Nellore, India. The study was conducted with 998 subjects (500 males and 498 females) and was approved by our Institutional ethics committee (Table 1). This study was undertaken over a period of one year in subjects with normal hepatic function and without complications of neuropathy, and retinopathy. The present study excludes patients with thyroid stimulating drugs, corticosteroids, lipid-lowering drugs, oral contraceptives, aspirin, sulphonamides, and pregnant women.

Specimen collection

Subjects under this study were advised to fast overnight (twelve hours). Blood samples were collected in the fasting condition. Venous blood (0.5 ml) collected from each subject was separated by centrifugation and stored at-20°C for further measurements. Hemolyzed and lipemic samples were avoided. For adequate quality control both normal, abnormal reference control serum solutions and calibrators were run before each testing. Other factors that influence the quality such as the proper functioning of instruments, quality of glassware, cuvettes and distilled water were taken care.

RESULTS

The serum uric acid (SUA) of the subjects was measured. The number of subjects in each age group follows a Gaussian normal distribution (the so-called bell curve), as expected in a large sample size of 998 subjects. The SUA data of the subjects were analyzed to determine the number of subjects with hyperuricemia, ≥6.5mg/dL for males and ≥6.0mg/dL for females), those with hypertension (HT) and diabetes mellitus (DM). 529 subjects (237 male, 292 female) were diagnosed with hyperuricemia (HU), 468 (256 male, 212 female) subjects were diabetic, while 504 (273 male, 231 female) subjects were hypertensive. Those with combinations of HU, DM and HT are shown in (Table 1).
Table 1: Details of the subjects of the study.

|                        | All subjects | Male subjects | Female subjects |
|------------------------|--------------|---------------|-----------------|
| Total subjects         | 998          | 500           | 498             |
| Diabetic (DM)          | 468          | 256           | 212             |
| Hypertensive (HT)      | 504          | 273           | 231             |
| Hyperuricemia (HU)*    | 529          | 237           | 292             |
| HU and DM              | 247          | 116           | 131             |
| HU and HT              | 286          | 136           | 150             |
| HU, HT and DM          | 143          | 76            | 67              |
| HU and HT/DM           | 390          | 176           | 214             |

*Male subjects with SUA ≥ 6.5 mg/dl and female subjects with SUA ≥ 6.0 mg/dl

Table 2 shows statistical analysis of serum uric acid levels 6.46 ± 1.79 Mean ± SD and p < 0.001 were statically significant (Table 2).

| Biochemical parameter | Mean ± SD (mg/dl) | T-value | P-value |
|-----------------------|-------------------|---------|---------|
| Serum uric acid       | 6.46 ± 1.79       | 96.4583 | <0.0001 |

The last column of (Tables 3) shows the number of subjects with HU and with either HT, DM or both, and increased risk of developing cardiovascular disease (CVD) due to HT and DM.

Table 4 shows the number has been arrived at by intersection of data sets of HU, HT and DM as indicated in the tables.

There were 176 male subjects and 214 female subjects have been determined to have HU along with HT or DM or both. Thus 390 out of 998 subjects or 39% of the total subjects, or 390 out of 529 with HU (74% of those with HU) of the study fall under the increased CVD risk category. The data in (Tables 3-5) have been analyzed age group wise.

Table 5 shows percentage of entire subjects within each age group with CVD risk, estimated from an intersection of datasets of hypertension (HT), diabetes mellitus (DM) and hyperuricemia (HU) The difference between the number of subjects with HU and HT/DM decreases with an increase in the age group.

Table 3 Male subjects with CVD risk (HU and HT/DM/both) in each age group, estimated from an intersection of datasets of hypertension (HT), diabetes mellitus (DM) and hyperuricemia (HU).

| Age group | HU | HU ∩ HT ∩ DM | HU ∩ HT | HU ∩ DM | HU and HT/DM/both* |
|-----------|----|--------------|---------|---------|-------------------|
| 15-24     | 4  | 1            | 2       | 1       | 2                 |
| 25-34     | 14 | 0            | 2       | 0       | 2                 |
| 35-44     | 41 | 1            | 14      | 12      | 23                |
| 45-54     | 52 | 18           | 33      | 25      | 40                |
| 55-64     | 55 | 20           | 36      | 31      | 47                |
| 65-74     | 59 | 27           | 38      | 37      | 48                |
| 75-84     | 13 | 7            | 11      | 9       | 13                |
| 85-94     | 2  | 0            | 0       | 1       | 1                 |
| Total     | 237| 76           | 136     | 116     | 176               |

HU and (HT or DM or both) = HU ∩ HT + HU ∩ DM - HU ∩ HT ∩ DM

Table 4: Comparison of age groups with hyperuricemia (HU), hypertension (HT) and diabetes mellitus (DM).

| Age group | HU | HU ∩ HT ∩ DM | HU ∩ HT | HU ∩ DM | HU and HT/DM/both* |
|-----------|----|--------------|---------|---------|-------------------|
| 15-24     | 7  | 0            | 1       | 2       | 3                 |
| 25-34     | 17 | 1            | 8       | 3       | 10                |
| 35-44     | 52 | 4            | 11      | 14      | 21                |
| 45-54     | 81 | 18           | 39      | 39      | 60                |
| 55-64     | 76 | 21           | 48      | 41      | 68                |
| 65-74     | 40 | 13           | 29      | 19      | 35                |
| 75-84     | 17 | 9            | 13      | 11      | 15                |
| 85-94     | 2  | 1            | 1       | 2       | 2                 |
| Total     | 292| 67           | 150     | 131     | 214               |

*HU and (HT or DM or both) = HU ∩ HT + HU ∩ DM - HU ∩ HT ∩ DM

The last column of (Tables 3-5) show the number of subjects with HU and with either HT, DM or both, and increased risk of developing cardiovascular disease (CVD) due to HT and DM. The number has been arrived
The data in (Tables 3-5) have been analyzed age group wise. Female subjects with CVD risk (HU and HT/DM/both) in each age group, estimated from an intersection of datasets of hypertension (HT), diabetes mellitus (DM) and hyperuricemia (HU). The number of female patients with HT, DM and HU, and the percentage of female subjects in the particular age group. Unlike the male subjects, the prevalence of HU is consistently more than HT and DM at all age groups in the female subjects. About 10% of female subjects in the 15-24 and 40% in the 25-34 age group are hypertensive, with 50% or more hypertensive in the higher age groups, except in the 85-94 age group where the population size is small. The SUA variation also follows the normal expected distribution with the highest number in the 6-7 mg/dl range. The mean and standard deviation were calculated for all the biochemical parameters. The significance between the groups was determined using Student t-test for equality of means. The two-tailed p-value is less than 0.0001 in the present study, which is statistically significant. The hypothetical mean is 1.0000, and the actual mean is 6.4600. The difference between these two values is 5.4600. The 95% confidence interval of this difference varies from 5.3489 to 5.5711. The values of other statistical parameters are as follows: t = 96.4583, df= 999, and standard error of difference = 0.057.

**DISCUSSION**

It is evident from (Table 1) that percentage of subjects with HU (53%), DM (37%) and HT (50%) is very large. The prevalence of HT and DM is more in male patients while the prevalence of HU is more in female patients. Since the age of the subjects varied from about 15 to over 90, it is also important to understand the percentage of people within each age group, not just the total subjects who are diagnosed with HU, HT and DM. It is seen that over 50% of all male patients in the 45-54 age group and above have HT and DM. Even in the relatively younger population in the 35-44 age group, this number is over 35% indicating the high prevalence of HT and DM in the population under study. Similarly, over 50% of the male subjects in the 55-64 and above age groups have hyperuricemia. The percentage of male subjects with HU is more than those with HT and DM in the 35-44 and below age groups, while those with HT are more than those with DM and HU in the older age groups. 390 of the 529 subjects with HU have HT or DM or both. Or 74% of those with HU have HT/DM/both, Pilger E, et al, Risk factors for peripheral atherosclerosis for HU retrospective evaluation by stepwise discriminant analysis was very significant number with increased CVD risk.\(^{20}\) The raw data was analyzed to determine these relationships for male, female and total subjects in each age group and presented in (Tables 3-5). It is evident from the large number of studies in the literature that hyperuricemia along with hypertension, diabetes mellitus or both is an indicator of increased risk of cardiovascular disease (CVD). The data normalized with respect to the total number of subjects in each age group. While the overall increased risk is for 39% of the total subjects, the number of subjects who fall under the CVD risk due to combined HU and HT/DM/both is 40% and above in the 45-54 age group. More females exist with HU and HT/DM/both in the 55-64 and above age groups than corresponding males. The percentage of males is, however, much higher in the 15-24 and 35-44 age groups. The data in the last column of (Tables 3-5) is normalized with respect to those with HU in each of the age groups is based on the entire population of subjects in each group. It can be seen from that more than 75% with HU in the 45-54 and above age groups also have HT/DM/both in

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**Table 5: Total subjects with CVD risk (HU and HT/DM/both) in each age group, estimated from an intersection of datasets of hypertension (HT), diabetes mellitus (DM) and hyperuricemia (HU) of all subjects.**

| Age group | HU | HU ∩ HT ∩ DM | HU ∩ HT | HU ∩ DM | HU and HT/DM/both* |
|-----------|----|--------------|---------|---------|-------------------|
| 15-24     | 11 | 1            | 3       | 3       | 5                 |
| 25-34     | 31 | 7            | 25      | 26      | 44                |
| 35-44     | 93 | 36           | 72      | 64      | 100               |
| 45-54     | 130| 41           | 84      | 72      | 115               |
| 55-64     | 131| 40           | 67      | 56      | 83                |
| 65-74     | 99 | 16           | 24      | 20      | 28                |
| 75-84     | 30 | 1            | 1       | 3       | 3                 |
| Total     | 237| 76           | 136     | 116     | 176               |

*HU and (HT or DM or both) =HU ∩HT+HU ∩DM-HU∩HT∩DM

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The relatively younger people within each age group, not just the total subjects or those with HU of the study fall under the increased CVD risk category.
both males and females and varies between 40-50% in the younger age group females and between about 15-60% in younger age group males. Schmidt MI et al, study shows dyslipidemia, hyperuricemia, diabetes, and hypertension and its association exists between HU and HT/DM has been observed in the present group of 998 subjects studied in this work. It is, however, not clear from the present study whether HU precedes HT/DM or the other way around since the increasing prevalence of HT/DM is also linked to increasing obesity and lifestyle-related changes in the Indian population. A relationship between hyperuricemia and CV disease has been established since the 1900's. Increased uric acid serum levels are a common finding in patients with high blood pressure, insulin resistance, obesity and CV disease. Bonora E et al, uric acid as a CV risk factor has been addressed in numerous prospective and cohort studies. Nevertheless, a debate arose from early times as to whether uric acid is an independent predictor of CV disease or not. It was later proven that both renal vasocostriction and various CV drugs- principally renin-angiotensin system suppressors and insulin-were associated with reduced urate excretion, further studies showed that it was more accurate to regard hyperuricemia as a consequence of the existence of previously related CV risk factors. Feig DI et al, study shows theorized that increased uric acid levels would be good based on antioxidant properties and positive outcomes on endothelial function were shown following the infusion of uric acid. On the other hand, an increase in blood pressure and increased salt sensitivity, stimulation of the renin-angiotensin system, and the development of insulin resistance would all have been beneficial in certain situations, such as tissue injury and ischemia. This controversy caused uric acid to be no longer regarded as a true CV risk factor. Majid A et al, shows increased awareness of the function of uric acid in cardio-renal disease, the discussion has resurfaced in the last years. In patients with heart failure, there is significant confirmation that elevated uric acid levels predict an increase in morbidity and mortality both in acute and chronic heart failure patients. Recent evidence has emerged in parallel suggesting uric acid is an inflammatory factor that also plays a role in endothelial dysfunction. Thus, uric acid can induce pro-inflammatory changes in the adipocyte that are similar to those observed in the pre-diabetic subject. Finally, most of these trials suggested that uric acid’s cardio-renal effects are due to its intracellular effects, unlike gout and stones. Therefore, practical conclusions regarding that relationship are that: Treatment with xanthine oxidase inhibitors may be most effective in reducing intracellular uric acid because they will block intracellular production as well as decrease extracellular levels. Siu YP et al, shows Only a reduced number of studies have shown recently that the use of allopurinol may be beneficial in terms of CV outcomes. However, because these data are few and the effects of allopurinol might not be limited to diminishing plasma uric acid levels, this point remains to be clarified with further studies. The novel febuxostat, a non-purine analogue inhibitor of xanthine oxidase, has proven to be effective in reducing serum uric acid levels in patients with hyperuricemia and gout arthropathy, however still uncertain, is its potential for reducing the risk of developing CV disease.

CONCLUSION

The study shows that a large percent of the male and female subjects of the study have either HT or DM with this reaching 45% and more in the particular age group in the 45-54 and above. Over 50% of patients in all age groups have been diagnosed with HU, except in the teens' group where the number is also an alarming 40%. The combined prevalence of HU, HT/DM is around 74% among all subjects with hyperuricemia, showing the high risk of CVD for this group. When only the subjects with HU are considered in each age group, the percentage at CVD risk is over 50% in the 35-44 age group. Evidence regarding the relationship between high serum uric acid concentrations and hypertension and other cardiovascular risk factors is extensive. Furthermore, current data also suggest that hyperuricemia could increase the risk of developing renal and CV disease. Nevertheless, it is too early to make clinical recommendations in regard to the benefits of using xanthine oxidase inhibitor allopurinol or the novel febuxostat in patients with asymptomatic increased uric acid levels and high CV risk. Further studies are needed to assess the exact role of uric acid reduction in the progression of cardio-renal events. Antihypertensive drugs can, however, modify the development of gout events in hypertensive patients, with losartan and calcium channel blockers having the greatest lowering effect on blood pressure because of their uricosuric properties.

ACKNOWLEDGEMENTS

Authors would like to thank the cooperation of our Department of General Medicine, Narayana Medical College and Hospital, Nellore, Andhra Pradesh, India.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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