HYPERURICEMIA AND TESTOSTERONE DEFICIENCY: AN UNDERESTIMATED CORRELATION

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Hyperuricemia and testosterone deficiency (TD) are two relatively common conditions in clinical practice. We conducted the present study on 9573 men to evaluate the association between the two conditions and establish a hypothetic explanation. Compared with the normal group, the hyperuricemia group has lower testosterone level (14.79 ± 5.55 vs. 17.12 ± 6.24, p < 0.001) and lower LH level (5.57 ± 3.31 vs. 5.75 ± 3.21, p = 0.003). There is a weak negative correlation between testosterone and serum uric acid (SUA) after adjusting for confounding factors (Spearman's Rho = -0.2, p < 0.001). On linear regression, serum uric acid corresponds to testosterone with the formula: Testosterone = -0.015 x SUA + 22.37. We hypothesize that the mechanism underlying testosterone deficiency in hyperuricemia patients is due to an inhibition of LH release of the pituitary. Further studies are needed to examine this hypothesis.

Keywords: Serum uric acid, hyperuricemia, testosterone deficiency.

I. INTRODUCTION

There is a rising concern about non-communicable conditions in Vietnamese men including hyperuricemia and TD. In men, testosterone is the major sex hormone that plays critical roles in developing secondary sexual characteristics and maintaining overall well-being. Low serum testosterone adversely affects multiple body systems and can cause a marked decrease in quality of life.[1] The testis mainly produces testosterone, and the pathway was controlled by the hypothalamus-pituitary-gonad (HPA) axis so that any dysfunction on the axis can result in a fluctuation in testosterone levels, mostly lower than the normal range. Uric acid is the end-product of purine metabolism in humans and higher primates. High blood concentrations of uric acid can lead to gout and are associated with other medical conditions, including diabetes and the formation of urate kidney stones.[2] A high uric acid level can be the result of the body making too much uric acid, not getting rid of enough of it or both.

Recent studies have demonstrated their mutual pathophysiology and both conditions are closely related to many other medical conditions such as MetS, cardiovascular diseases, diabetes, obesity, etc. [3–5] However, research assessing the causal relationship between low testosterone and hyperuricemia has shown to be inconclusive. Approaching these conditions individually may not produce effective results. The presence of hyperuricemia might exacerbate TD. On the other hand, when low testosterone is left treated incompletely, it can worsen uric acid disorder and lead to joint and kidney complications. Gao et al. indicated that men with higher UA concentrations had significantly lower TT, FSH, LH and SHBG levels.[6] In contrast, a prospective cohort study showed that a low testosterone level was associated with an elevated SU level and gout risk subsequently.[7] Therefore, investigating the association between hyperuricemia and

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TD is critical for managing and treating both conditions. Given the aforementioned facts, we conducted this study with the aim to investigate the correlation between hyperuricemia and TD in Vietnamese men.

II. MATERIALS AND METHODS

1. Subjects

The study was conducted on men seeking consultation at the Department of Andrology and Sexual Medicine - Hanoi Medical University Hospital from January 2014 to December 2021.

The inclusion and exclusion criteria for the study were as follows:

Inclusion criteria:

- Male over 16 years old

- Blood samples available to evaluate reproductive hormones and biochemical parameters.

- Height and weight measurement in the same session as the blood test was taken.

Exclusion criteria:

- Male taking medications that affect the production and excretion of uric acid in the blood within ten days, such as allopurinol, probenecid, sulfinpyrazol, salicylates, phenylbutazol, ascorbic acid, ethambutol...

- Male who have been diagnosed and treated for gout, patients with end-stage chronic renal failure on hemodialysis or cirrhosis.

- Male who were on endocrine medications or medications/substances enhancing reproductive function.

- Male with malignancies or undergoing chemotherapy or radiation therapy.

2. Methods

Study design:

Descriptive cross-sectional study

Sample size and sampling method

Convenience sampling with 9573 men were recruited.

Study process:

Medical history was obtained from male who visited for andrological diseases clinical examination was performed according to hospital routine procedure. Subsequently, subjects would be counseled to have blood samples collected for hormone profiles and biochemical parameters assessment.

Levels of sex hormones were determined by the electroluminescent immunoassay method "ECLIA" used for Cobase immunoassay machines. The test kit was manufactured and supplied by Roche. The tests were based on a competitive testing principle using a specific high-affinity monoclonal antibody directed against the hormone.

Fasting blood samples were collected in the morning between 8-11 am and serum was referred to the laboratory for testing. Reference values of hormonal parameters were provided by the Laboratory Department of Hanoi Medical University Hospital.

Table 1. Reference values of the laboratory department of Hanoi Medical University Hospital

Parameters	Unit	Reference values
Uric acid	µmol/L	202.3 - 416.5
LH	mU/mL	1.7 - 8.6
FSH	mU/mL	3.5 - 12.5
Total testosterone	nmol/L	9.9 - 27.8

Hyperuricemia is defined as a SUA level ≥ 420 µmol/L (in men).

TD is defined as a total testosterone level < 12 nmol/L.[8]

3. Data analysis

R software version 3.6.1 for Windows operating system was used to analyse the data. The normality of the distribution was tested using the Kolmogorov-Smirnov algorithm. All quantitative parameters were presented as mean ± standard deviation, median, percentile, minimum, and maximum values. For continuous variables, the difference between the two groups was assessed by Student's t-test for normal distribution and the Mann-Whitney U-test for non-normal distribution. The correlation between SUA and other parameters was determined using Spearman's rank correlation analysis. Statistical significance was set at $p < 0.05$.

4. Ethical considerations

The study was approved by the Board of Directors of Hanoi Medical University Hospital. Information of study participants was kept confidential. Data were for research purposes only.

III. RESULTS

From January 2014 to December 2021, 9573 participants aged 16-85 years old were recruited in the study.

Table 2. General characteristics of the subjects

Characteristics	N	%	Mean	SD	Median	Min-Max
Age (years old)	9573		38.91	12.98	36	16 - 85
<30	2812	29.37				
30-39	2813	29.38				
40-49	1824	19.05				
≥ 50	2124	22.19				
Height (cm)	9573		167.16	5.67	167	147 - 190
Weight (kg)	9573		64.55	8.67	64	40 - 110
BMI (kg/m²)	9573		23.07	2.66	23.03	15.05 - 38.51
<18.5	350	3.66				
18.5-22.99	4393	45.89				
23-24.99	2725	28.47				
≥25	2105	21.99				
Smoking	9573					
Yes	2299	24.01				
No	7274	75.99				

The mean age of the subjects was 38.91 ± 12.98 years old, the age groups were distributed relatively evenly. The mean height and weight of the subjects were 167.16 ± 5.67 cm and 64.55 ± 8.67 kg. The proportion of overweight subjects (23 ≤ BMI < 25) was 28.47% and obese subjects (BMI ≥ 25) was 21.99%. About one-quarter of the study subjects were smokers.

Table 3. Association between hyperuricemia and other characteristics

Characteristics	Uric acid levels		p
	Hyperuricemia (n = 2891)	Normal (n = 6682)	
Age (years old)	38.49 ± 13.21	39.1 ± 12.88	**0.017**
<30	907 (31.37)	1905 (28.51)	**0.011**
30-39	853 (29.51)	1960 (29.33)	
40-49	509 (17.61)	1315 (19.68)	
≥ 50	622 (21.52)	1502 (22.48)	
BMI (kg/m^2)	23.93 ± 2.63	22.69 ± 2.59	**<0.001**
<18.5	43 (1.49)	307 (4.59)	**<0.001**
18.5-23	994 (34.38)	3399 (50.87)	
23-24.99	956 (33.07)	1769 (26.47)	
≥ 25	898 (31.06)	1207 (18.06)	
Smoking			
Yes	681 (25.56)	1618 (24.21)	0.48
No	2210 (76.44)	5064 (75.79)	
LH (mUI/mL)	5.57 ± 3.31	5.75 ± 3.21	**0.003**
FSH (mUI/mL)	6.01 ± 5	6.11 ± 5.25	0.21
Estradiol(mUI/mL)	109.41 ± 46.58	109.28 ± 46.76	0.55
Testosterone	14.79 ± 5.55	17.12 ± 6.24	**<0.001**
<12nmol/L	957 (33.1)	1343 (20.1)	**<0.001**
≥12 nmol/L	1934 (66.9)	5339 (79.9)	

Males with hyperuricemia had a higher rate of overweight and obesity than patients with SUA levels within the normal range. Similarly, the proportion of hyperuricemic subjects with TD (testosterone <12 nmol/L) was significantly higher than those with normal testosterone levels ($p < 0.001$). In other comparisons, the differences between the two groups were not statistically significant.

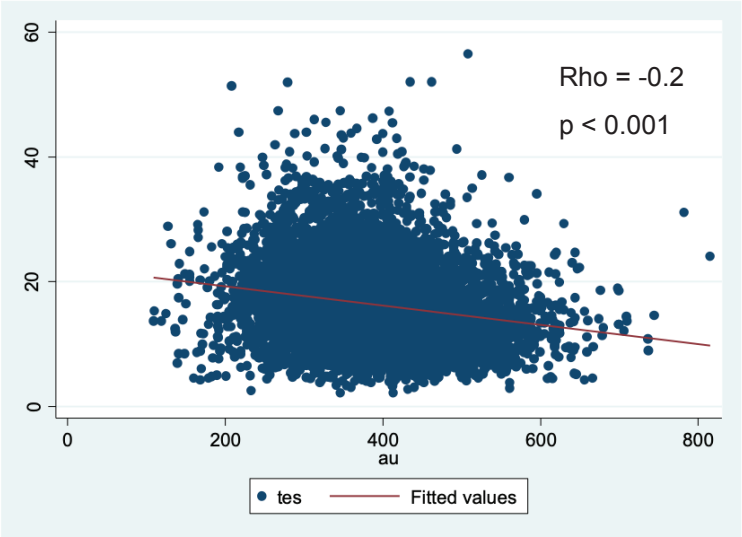

Figure 1. Correlation of testosterone and uric acid

There was a weak negative correlation between testosterone and SUA. SUA corresponded to testosterone with the formula: Testosterone = -0.015 x SUA + 22.37; with each unit increase in SUA, testosterone decreases by 0.015 unit (p<0.001).

IV. DISCUSSION

Testosterone deficiency, though accounted for a considerable prevalence, has not been well studied and managed in Vietnam.[9] Recent evidence has shown an increase in TD which was associated with metabolic disorders in light of lifestyle changes and quality of life. Among those disorders, hyperuricemia is predominant in men and may cause a detrimental effect on physiological functions of reproductive glands. To our knowledge, the present study is one of the first studies with a large sample size regarding the association between SUA and testosterone in the Vietnamese population.

In this study, we evaluated the association between SUA and testosterone levels among 9573 men from January 2014 to December 2021. Among the study subjects, overweight and obese patients accounted for 50,46%. The percentage was significantly higher in hyperuricemia group (64.13% vs. 44.63%, p<0.001). The relatively high rate of overweight and obesity in patients with hyperuricemia requires more attention to the lipid profile in particular and metabolic and cardiovascular problems in general. Saito et al. indicated elevated SUA as a risk factor of cardiovascular diseases and other metabolic disorders.[10]

We found a negative correlation between testosterone and uric acid levels in univariate and multivariate linear regression analyses. This correlation remained significant after removing subjects with outliers and extreme values. Our results were consistent with several previous studies. Fukai et al. conducted a cross-sectional study on 139 middle-aged Japanese male patients and found a negative correlation between serum testosterone and uric acid levels (p<0.05), but no correlation between free testosterone and uric acid levels.[11] Krysiak et al. investigated 51 men with diabetes, found that testosterone levels were negatively correlated with SUA, and the combination of testosterone

replacement and metformin reduced uric acid levels significantly compared with the group using metformin only ($p<0.05$) and the group on testosterone - glimepiride combination ($p<0.05$). The study also reported that the level of uric acid reduction in the group receiving testosterone correlated with the reduction of HOMA1-ir.[12] Another study on 1026 diabetic patients indicated that there was an inverse correlation of uric acid with testosterone and sex hormone binding globulin (SHBG) levels while uric acid and dehydroepiandrosterone (DHEA) levels were positively correlated. In addition, this study noted that when uric acid level was elevated, both LH, FSH, and testosterone levels declined.[13]

In the hyperuricemia group, testosterone levels were significantly lower ($p<0.01$). We also found a significant decrease in LH levels compared with the non-hyperuricemia group ($p < 0.05$), while there were no difference in levels of FSH and estradiol between the two groups. It led us to hypothesize that the mechanism underlying low testosterone levels in hyperuricemia is not due to the effect of estradiol but another hormone that inhibits LH secretion of the pituitary gland.

Testosterone, the predominant sex hormone in males, is produced primarily in testicular Leydig cells under the control of the hypothalamus (via GnRH) and the pituitary gland (via LH). In healthy men, most circulating testosterone (98%) is bound, either to sex-hormone binding globulin (SHBG; 60%) or to lower affinity, high-capacity binding proteins (predominantly albumin; 38%), with approximately 2% being free of any binding. The physiological effects are only exhibited by bioavailable testosterone, comprising the free testosterone (2%) and the low affinity bound one (38%). Total T concentrations are about 10-30 nmol/L at age 30 years in men and decline at an average rate of 1-2% per year with aging.[14]

Several mechanisms of the relationship between serum testosterone and SUA have been proposed. It is hypothesized that the decreased blood testosterone levels cause insulin resistance in extrarenal tissues. In response to systemic insulin resistance, pancreatic hypersecretion leads to a prolonged increase in insulin levels in the blood. This phenomenon subsequently enhances the effect of insulin on the kidneys, thereby inhibiting the secretion and increasing the reabsorption of urate in the renal tubules induce elevated serum uric acid levels eventually.[13] Hyperuricemia, in its turn, may accelerate the synthesis of estradiol from testosterone by aromatase. In addition, the release of pro-inflammatory chemicals such as IL-1, IL-6, TNF-α, and leptin which decrease GnRH secretion impulse, LH secretion, and the response of Leydig cells to LH, thereby ultimately reducing testosterone synthesis and secretion.[17] Metabolic syndrome, systemic insulin resistance, and obesity may intervene with both pathways, leading to the pathological spiral of hyperuricemia and TD.

Our study was not without limitations. Firstly, not all subjects in our study had their testosterone levels measured twice to confirm TD, due to the outpatient clinical setting. However, as the samples were taken in the morning and after fasting, it guaranteed the accuracy of testosterone deficiency diagnosis. Secondly, the outpatient clinic setting prevented us from controlling factors affecting SUA, such as excessive alcohol and purine-rich foods consumption before the session. Lastly, due to its cross-sectional design, our study could only hypothesize the association between hypouricemia and TD. In the future, a prospective study is necessary to prove the

relationship as well as evaluate the influence of components of metabolic syndrome on it.

V. CONCLUSION

There was a significantly negative correlation between testosterone and SUA. Hyperuricemia men were more likely to be overweight, hypogonadal and have lower levels of LH. We hypothesize that the mechanism underlying TD in hyperuricemia men is due to an inhibition of LH secretion. Further prospective studies are warranted to examine this hypothesis.

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