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ORIGINAL ARTICLE

Gender impact on the correlations between Graves' hyperthyroidism and hyperuricemia in Chinese

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Abstract

Objective An increased level of serum uric acid (SUA) can be observed in patients with hypothyroidism. Nonetheless, data on the relationship between hyperuricemia and hyperthyroidism was still controversial. Thus, we aimed to analyze the association between Graves' hyperthyroidism and hyperuricemia in Chinese men and women.

Methods We recruited 103 male and 254 female patients with Graves' hyperthyroidism, as well as the same number of control subjects. Anthropometric measurements and fasting blood tests were collected and analyzed statistically by binary logistic regressions to determine the risk of developing hyperuricemia in hyperthyroidism.

Results SUA levels in males were significantly higher than that in females in both patients and controls. SUA levels were also significantly increased in hyperthyroid patients compared to in controls in both genders. The incidence of hyperuricemia rose significantly in subjects with hyperthyroidism with a higher prevalence in males than in females. SUA was negatively correlated with age and fasting glucose in male hyperthyroid patients, while it was positively correlated with body height, body weight, free triiodothyronine, and free thyroxine in female patients. Hyperthyroidism was a risk factor for hyperuricemia with an odd ratio of 4.536 for men and 2.730 for women.

Conclusions For hyperuricemia, hyperthyroidism was an important risk factor that should not be neglected, especially for men.

Keywords Gender · Graves' disease (GD) · Hyperthyroidism · Hyperuricemia · Serum uric acid (SUA)

Introduction

As the end metabolic product of purine nucleotide, uric acid could be influenced by thyroid hormones. An increased level of serum uric acid (SUA) has been observed in patients with hypothyroidism, which is reportedly to be caused by a reduction in renal plasma flow and glomerular filtration rate (GFR) [1–8]. However, relationship between hyperuricemia and hyperthyroidism is still inconsistent [7–14]. Some reports demonstrated that hyperuricemia could happen in hyperthyroidism, which is probably due to the accelerated purine nucleotide turnover for uric acid production [7–12, 15]. On the other hand, See et al. [7] found both hyperthyroid and hypothyroid status were significantly associated with gout but only weakly associated with hyperuricemia. Raber et al. [13] did not find significant difference in SUA between cases with hyperthyroidism and cases with euthyroidism, and concluded that routine determination of SUA in hyperthyroid patients was not warranted. Meuwese et al. [14] showed in older persons, an association between thyroid status and change in renal function over time was absent. Besides this controversy, the impact of gender on this relationship has scarcely been explored. Therefore, the objective of this cross-sectional study was to investigate the correlation between Graves' hyperthyroidism and hyperuricemia with emphasized focus on differences resulting from different genders.

Xuehui Liu and Jianping Zhang contributed equally to this work.

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Subjects and methods

Recruitment

This study was carried out under the collaboration from the Departments of Nuclear Medicine and Health Management in Tianjin Medical University General Hospital, and Department of Nuclear Medicine in Tianjin Third Central Hospital. From March 2014 to March 2015, 254 hyperthyroid females (aged from 17 to 73 years) and 103 hyperthyroid males (aged from 18 to 75 years) were recruited.

All patients were diagnosed with Graves' disease (GD) on the basis of clinical manifestations and laboratory criteria. [16, 17] Inclusion criteria are as follows: symptoms of higher metabolism, increased free thyroid hormones and decreased thyroid-stimulating hormone (TSH), elevated ^{131}I uptake value, with or without signs of diffuse goiter, exophthalmos, and pretibial myxedema. Thyrotropin recepter antibody, thyroglobulin antibody, and thyroid peroxidase antibody were tested in all cases. Thyroid ultrasound examination and thyroid scintigraphy were also performed to assess thyroid structure and exclude multinodular goiter or other causes of hyperthyroidism (Plummer's disease). In order to limit the analysis on the direct relationship between thyroid hormone and SUA, exclusion criteria also applied to GD cases with no comorbidities (e.g., cardiovascular, renal, hepatic, gastrointestinal, or oncological diseases). As for the control group, 254 healthy females and 103 healthy males were recruited whose age and body mass index (BMI) were matched with the patient group for either sex. The control participants were enrolled from our community-based health check program as conducted previously by our group [18–29]. No participant had known thyroid, cardiovascular, renal, hepatic, gastrointestinal, or oncological diseases. The Institutional Review Board of Tianjin Medical University General Hospital approved the ethical, methodological and protocol aspects of this investigation. All participants provided their written informed consents.

Parameters

Each participant received anthropometric measurements and fasting blood tests during his/her visit to our institution. Physical examination included body height (BH), body weight (BW), and blood pressure. BMI was calculated as BW divided by BH squared (kg/m^2). SUA, creatinine (Cr), blood urea nitrogen (BUN), and fasting glucose (FG) were determined enzymatically by an auto-analyzer (Hitachi Model 7170 analyzer, Hitachi, Tokyo, Japan). TSH, free thyroxine (FT4), and free triiodothyronine (FT3) were analyzed on a fully automated ADVIA Centaur analyzer (Siemens Healthcare Diagnostics, New York, USA) by chemiluminescent reaction principle.

Definitions

Hyperuricemia was defined as a SUA level of higher than 420 μmol/L in men, and higher than 360 μmon/L in women [18, 19, 21]. We calculated the estimated glomerular filtration rate (e-GFR) for every participant. The modified equation for Chinese was used [30]: e-GFR = $186 \times (\mathrm{Cr}^{-1.154}) \times (\mathrm{age}^{-0.203}) \times 1.233$ (for Chinese) × 0.742 (if female).

Statistical analysis

Data were analyzed based on different gender. Differences of indices between groups were analyzed by independent samples *t* test. Chi-square test was used to compare inter-group prevalence differences. Pearson bivariate correlation was made between SUA and other variables. Compared with control groups, odds ratio (OR) for developing hyperuricemia with 95% confidence interval (CI) was calculated by a binary logistic regression model. Statistical Package for Social Sciences (SPSS version 17.0, Chicago, IL, USA) was used to conduct statistics and significance was defined as a *P* value of lower than 0.05.

Results

For each gender, age and BMI were strictly matched between participants with hyperthyroidism and euthyroidism, and no significant differences were shown. Generally, in both genders, patients with hyperthyroidism showed significantly increased levels of FG, BUN, SUA, and e-GFR, and significantly suppressed Cr than in controls (Table 1). In addition, levels of BUN, Cr, and SUA were all significantly higher in males than in females, no matter which thyroid state they were in. However, no significant difference was shown in e-GFR between genders. It was worthwhile to note that averages of all the above mentioned parameters were in normal ranges. The prevalence of hyperuricemia was significantly increased in patients of hyperthyroidism, with males substantially higher than females (Table 2).

Correlation coefficients between SUA and other variables were calculated to determine if any associations existed (Table 3). We demonstrated significant positive correlations between SUA and BH and Cr, yet negative correlations between SUA and age and FG in men. For women, SUA was significantly positively correlated with BH, BW, FT3, and FT4. Subsequently, we investigated the risk of developing hyperuricemia in a hyperthyroid status by using a binary logistic regression model. In the model, we designated two thyroid functional status (hyperthyroidism versus euthyroidism) as the categorical variable, and included age, BMI, and FG as covariates. We showed an OR of 2.730 (1.508–4.945) for females and a higher OR of 4.536 (1.848–11.129) for males, both OR had

Table 1 Comparisons of measured variables between hyperthyroidism and controls

	Male		Female	
	Hyperthyroidism	Controls	Hyperthyroidism	Controls
Age (years)	40.84 ± 15.40	40.84 ± 15.41	40.93 ± 13.94	41.15 ± 13.64
BMI (kg/m^2)	22.41 ± 2.98	22.54 ± 2.71	22.22 ± 3.12	22.29 ± 2.93
BH (m)	1.71 ± 0.07 ^^	1.73 ± 0.06 ^^	1.61 ± 0.06	1.60 ± 0.06
BW(kg)	65.69 ± 9.71^^	67.20 ± 9.15 ^^	57.92 ± 8.94	57.44 ± 8.41
FT3 (pmol/L)	22.32 ± 8.28 **	5.41 ± 0.51^^	21.79 ± 8.74 **	4.94 ± 0.49
FT4 (pmol/L)	68.66 ± 37.36 **	17.26 ± 1.85 ^^	68.42 ± 40.17 **	15.65 ± 1.94
TSH (μlU/mL)	0.017 ± 0.082 **	1.957 ± 0.929 ^^	0.013 ± 0.078 **	2.326 ± 1.016
FG (mmol/L)	5.98 ± 1.80 **	5.25 ± 1.67	5.65 ± 0.93 **	4.97 ± 0.74
BUN (mmol/L)	5.42 ± 1.42 ** ^^	4.78 ± 1.40 ^^	4.63 ± 1.27 **	4.34 ± 1.25
Cr (μmol/L)	52.91 ± 13.99 ** ^^	80.19 ± 11.54 ^^	39.75 ± 9.69 **	64.74 ± 13.11
SUA (μmol/L)	366.51 ± 90.98 * ^^	341.25 ± 57.97 ^^	298.23 ± 76.58 **	273.28 ± 68.66
e-GFR (ml/min per 1.73m^2)	218.01 ± 75.58 **	126.49 ± 26.37	220.72 ± 68.45 **	121.76 ± 28.14

BMI body mass index, *BH* body height, *BW* body weight, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid stimulation hormone, *FG* fasting blood glucose, *BUN* blood urea nitrogen, *Cr* creatinine, *SUA* serum uric acid, *e-GFR* evaluated glomerular filtration rate

* $P < 0.05$, ** $P < 0.01$ compared between euthyroidism and hyperthyroidism in both genders

^^ $P < 0.01$ compared between different gender of the same thyroid state

significance. These results had twofold meanings. First, hyperthyroidism was a risk factor for developing hyperuricemia. Second, men possessed greater risk than women.

Discussion

There has been a debate about whether hyperthyroidism is a risk factor for hyperuricemia, although the majority of previous reports were in favor of this statement [7–14]. Previous studies showed that SUA increased in patients with hyperthyroidism, while its average was still within the normal range [8–12]. In addition, some researchers noticed that hyperuricemia caused by hyperthyroidism was weaker than that caused by hypothyroidism [8]. In our previous health screening program study, significantly elevated risk for hyperuricemia was only observed in mild hypothyroidism male participants, whereas no statistical risk was found in female, and no meaningful risk was found in mild hyperthyroidism participants neither [21]. In this investigation, we aimed to provide more evidence to demonstrate the likelihood of hyperthyroid hyperuicemia with the largest sample size among similar researches. This paper also analyzed the topic from the perspective of gender impact. In our previous work, mild hyperthyroidism was defined as TSH less than 0.3 μIU/mL as well as lacking of hypermetabolic symptoms. They were selected from the cohort of physical examination. However, the cohort of this study were patients with clinical GD, complaining obvious hypermetabolic symptoms, such as palpitation, fatigue, and hand tremor. There was no overlap between these two groups of patients.

The current study showed that SUA concentration was significantly increased in hyperthyroid patients than in controls in both genders (Table 1), which was consistent with previous studies [8–12]. We also found that the average SUA level of male was significantly greater than that of female in participants with

Table 2 Hyperuricemia prevalence among hyperthyroidism and controls

	Male				Female			
	Hyperthyroidism		Controls		Hyperthyroidism		Controls	
	Count	Prevalence (%)	Count	Prevalence (%)	Count	Prevalence (%)	Count	Prevalence (%)
Hyperuricemia	26	25.2% *	8	7.8%	48	18.9% *	22	8.7%
Normal uric acid	77	74.8%	95	92.2%	206	81.1%	232	91.3%

*$P < 0.01$, hyperuricemia prevalence compared between hyperthyroidism and controls

Table 3 Pearson bivariate correlation between SUA and other variables

	Male (correlation coefficients)	Female (correlation coefficients)
Age	−0.285 **	−0.122
BMI	−0.032	0.103
BH	0.256 **	0.154 *
BW	0.104	0.162 **
FT3	0.047	0.231 **
FT4	0.112	0.237 **
TSH	−0.037	−0.005
FG	−0.208 *	−0.108
BUN	0.023	0.086
Cr	0.204 *	0.101
e-GFR	−0.117	−0.017

SUA serum uric acid, *BMI* body mass index, *BH* body height, *BW* body weight, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid stimulation hormone, *FG* fasting glucose, *BUN* blood urea nitrogen, *Cr* creatinine, *e-GFR* evaluated glomerular filtration rate

*$P < 0.05$, ** $P < 0.01$

hyperthyroidism as well as in controls (Table 1). The incidence of hyperuricemia rose significantly in subjects with hyperthyroidism than in controls, and we demonstrated a higher prevalence in male than in female as well (Table 2). The mechanism of the above identified gender diversity could be ascribed to the sex hormone estrogen, which had a strong protective effect for hyperuricemia [21, 31, 32].

In our study, SUA was positively correlated with BH and Cr, and negatively correlated with age and FG in male patients with hyperthyroidism, while it was positively correlated with BH, BW, FT3, and FT4 in female patients (Table 3). The negative correlation with age in men meant that male patients with hyperthyroidism should receive monitoring of SUA, especially for young patients. The positive linear correlation with thyroid function (FT3 and FT4) in women indicated, in female patients with higher levels of thyroid function, monitoring SUA should be more necessary.

In the current study, a significantly elevated risk of hyperuricemia was observed in the hyperthyroid participants. Mechanistically, various metabolic processes are accelerated in hyperthyroid state due to GD, including purine metabolism [15]. Fukui et al. [15] indicated that the enhanced activity of the purine nucleotide cycle was probably due to the following reasons: 1) an increase in ATP consumption due to the augmented basal metabolic rate; 2) the acceleration of AMP deaminase activity by the conversion of muscle fiber type; and 3) a poor supplementation of ATP due to the low glycogen content and reserve in GD. As for the renal uric acid clearance, conflicting hypothesis exist. For instance, Sato et al. [10] found that renal uric acid clearance was increased in patients with GD. Yet, increased uric acid production surmounted the increase in its clearance, resulting in increased SUA as a net effect. However, Shiroba et al. [11] sustained that direct action of thyroxin on the kidney was a decrease in uric acid tubular excretion. Our second finding regarding risks of hyperthyroid hyperuricemia was that hyperthyroidism was an explicit risk factor especially for men. We showed an OR of 2.730 in females and a dramatically higher OR of 4.536 in males. We considered that the protective effect of estrogen in females could be the underlining reason. In fact, in our previous study, mild hypothyroidism was found to be a risk factor for hyperuricemia in males while it was not in females, which phenomenon should also be attributed to the protective effect of estrogen [21]. In addition, we believed that there are multiple factors that could cause the reported discrepancies about hyperthyroid hyperuricemia included [7, 13, 14]: study population characteristics, sample size, laboratory methods for parameter measurements, and definition of hyperthyroidism, which opinions were also shared by Ye et al [33] For instance, negative findings in a Netherland study were based on a population with a baseline age of higher than 85 years old [14]. And the mean ages from the Taiwan study [7] and the Austria study [13] were 53 and 48 years old respectively. The mean age of our recruited population was just about 41 years old. As indicated by Meuwese et al. [14], when people grow old, age-related adaptation and regulation of the hypothalamic-pituitary-thyroid axis, metabolic rate, renal function, and eGFR could result in the negative correlation between thyroid function and uric acid.

For the correct interpretation of our results, some limitations have to be discussed. First, this was a cross-sectional study, which could not determine causality effect. A prospective longitudinal study on the relationship between hyperthyrodism and hyperuricemia would be important to confirm the results. Second, more participants should be included for better stratifications of confounding factors. Third, we assayed SUA and thyroid hormones on a single measurement due to budget restrictions. And last but not least, although we ruled out cases with co-morbidities, there could be some cases with just ostensible healthy circumstance, meaning that there could be some undetected medical conditions that could alter SUA levels. There could also happen that participants might not report all drugs they took like simply aspirin. Aspirin is known to have a bimodal effect on the renal handling of uric acid. High dosages (> 3 g/day) are uricosuric, while low dosages (1–2 g/day) cause serum uric retention [34]. These shall require special attention in future studies.

Conclusion

This study systematically analyzed the associations between hyperthyrodism and hyperuricemia in males and females. We concluded that, for hyperuricemia, hyperthyroidism was an important risk factor that should not be neglected, especially for men.

Author contributions statement Zhaowei Meng and Jian Tan designed the investigation.

Xuehui Liu, Jianping Zhang, Zhaowei Meng, Qiang Jia, Guizhi Zhang, Xue Li, Na Liu, Tianpeng Hu, Pingping Zhou, Qing Zhang, Kun Song, and Qiyu Jia conducted the investigation and collected data.

Jianping Zhang, Zhaowei Meng, and Xue Li performed the statistics.

Jianping Zhang, Zhaowei Meng, and Xue Li wrote the main manuscript.

All authors reviewed and proved the manuscript.

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Compliance with ethical standards

Conflict of interest

Xuehui Liu declares that he has no conflict of interest.

Jianping Zhang declares that she has no conflict of interest.

Zhaowei Meng declares that he has no conflict of interest.

Qiang Jia declares that he has no conflict of interest.

Jian Tan declares that he has no conflict of interest.

Xue Li declares that she has no conflict of interest.

Guizhi Zhang declares that she has no conflict of interest.

Na Liu declares that she has no conflict of interest.

Tianpeng Hu declares that he has no conflict of interest.

Pingping Zhou declares that she has no conflict of interest.

Qing Zhang declares that she has no conflict of interest.

Kun Song declares that he has no conflict of interest.

Qiyu Jia declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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