Correlation Between Serum Thyroid Hormone Levels and Hyperuricemia in Euthyroid Hypertensive Patients (Postprint)

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Abstract

Abstract Background: Serum uric acid (SUA) is closely associated with the occurrence and development of hypertension, and hypertensive patients often exhibit concomitant thyroid function alterations. However, there have been few reports on the correlation between thyroid hormone levels and the risk of hyperuricemia (HUA) in hypertensive patients with normal thyroid function. Objective: To investigate the correlation between serum thyroid hormone levels and HUA in essential hypertension (EH) patients with normal thyroid function. Methods: A total of 267 EH patients with normal thyroid function admitted to the Department of Cardiology, Xianyang Hospital of Yan' an University between January 2019 and December 2020 were retrospectively enrolled as study subjects. Based on the presence or absence of comorbid HUA, they were divided into a non-HUA group (n=166) and a HUA group (n=101). Basic characteristics, SUA, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels were compared between the two groups, and Pearson correlation analysis and multivariate Logistic regression analysis were conducted. Results: The HUA group exhibited higher proportions of males, body mass index (BMI), diastolic blood pressure (DBP), number of smokers, number of drinkers, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), SUA, and FT3 levels, and lower age compared with the non-HUA group (all $P<0.05$). Multivariate Logistic regression analysis revealed that male gender was associated with higher risk of HUA compared with female gender, and elevated BMI, TG, LDL-C, FT3, Scr levels and age were independent influencing factors for HUA development in EH patients [OR (95% CI) 2.843 (1.121-7.215), 1.126 (1.020-1.234), 1.824 (1.300-2.560), 2.804 (1.157-6.795), 2.297 (1.326-3.977), 1.071 (1.041-1.102), 0.959 (0.931-0.989)]. Pearson correlation analysis demonstrated that FT3 level was positively correlated with SUA in EH patients ($r=0.327$, $P<0.001$). Conclusion:

Serum FT3 level is elevated in EH patients with normal thyroid function and comorbid HUA compared with those without HUA, and increased serum FT3 level is closely associated with HUA occurrence in EH patients, which warrants clinical attention.

Full Text

Correlation Between Serum Thyroid Hormone Levels and Hyperuricemia in Euthyroid Hypertensive Patients

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Abstract

Background: Serum uric acid (SUA) is closely associated with the development and progression of hypertension, and hypertensive patients often experience alterations in thyroid function. However, few studies have investigated the relationship between thyroid hormone levels and hyperuricemia (HUA) risk in hypertensive patients with normal thyroid function.

Objective: To explore the correlation between serum thyroid hormone levels and HUA in euthyroid patients with essential hypertension (EH).

Methods: We retrospectively enrolled 267 euthyroid EH patients admitted to the Department of Cardiology at Xianyang Hospital of Yan' an University between January 2019 and December 2020. Based on the presence or absence of HUA, patients were divided into a non-HUA group (n=166) and a HUA group (n=101). Baseline characteristics, SUA, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels were compared between groups, followed by Pearson correlation analysis and multivariate logistic regression analysis.

Results: The HUA group exhibited significantly higher proportions of male patients, body mass index (BMI), diastolic blood pressure (DBP), smoking and drinking rates, as well as elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), SUA, and

FT3 levels compared to the non-HUA group, while age was significantly lower (all P<0.05). Multivariate logistic regression analysis revealed that male sex, elevated BMI, TG, LDL-C, FT3, Scr levels, and younger age were independent risk factors for HUA in EH patients [OR (95% CI): 2.843 (1.121–7.215), 1.126 (1.020–1.234), 1.824 (1.300–2.560), 2.804 (1.157–6.795), 2.297 (1.326–3.977), 1.071 (1.041–1.102), and 0.959 (0.931–0.989), respectively]. Pearson correlation analysis demonstrated a positive correlation between FT3 levels and SUA in EH patients (r=0.327, P<0.001).

Conclusion: Euthyroid EH patients with HUA have higher serum FT3 levels than those without HUA. Elevated FT3 levels are closely associated with HUA development in EH patients and warrant clinical attention.

Keywords: Essential hypertension; Thyroid function; Thyroid hormone; Hyperuricemia

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Introduction

Uric acid (UA) is the final degradation product of purine compounds, produced by the liver and excreted primarily by the kidneys (65–75%) and gastrointestinal tract (25–35%) [1,2]. Hyperuricemia (HUA) occurs when increased UA production and/or decreased excretion leads to elevated serum uric acid (SUA) levels [3]. Although not a fatal disease, HUA is a common metabolic disorder closely linked to cardiovascular disease and chronic renal failure [4,5]. Studies have reported a high prevalence of HUA among patients with essential hypertension (EH) in China [6], with nearly 90% of hypertensive adolescents exhibiting elevated SUA levels that correlate positively with systolic blood pressure [7]. Early identification and intervention of HUA risk factors in EH patients is therefore crucial.

Thyroid dysfunction has long been recognized as closely related to HUA [8]. Both hyperthyroidism and hypothyroidism patients show elevated SUA levels [9,10], and exogenous thyroxine supplementation can reduce SUA levels in subclinical hypothyroidism patients [11], suggesting a relationship between thyroid hormone levels and SUA. Recent studies have examined thyroid hormone levels and HUA in subjects without overt thyroid dysfunction [12]. However, research on the association between thyroid hormone levels and HUA risk in euthyroid EH patients remains scarce. This study therefore investigated thyroid hormone levels and HUA risk in euthyroid EH patients by comparing thyroid hormone profiles between non-HUA and HUA patients.

Methods

Study Population We retrospectively selected 267 euthyroid EH patients hospitalized in the Department of Cardiology at Xianyang Hospital of Yan' an University between January 2019 and December 2020. Patients were divided

into a non-HUA group (n=166) and a HUA group (n=101) based on HUA status. Inclusion criteria were: (1) primary hypertension diagnosis; (2) normal thyroid function; and (3) age $ $18 years. Exclusion criteria included: (1) secondary hypertension; (2) severe cardiovascular or cerebrovascular diseases (coronary artery disease, heart failure, arrhythmia, congenital heart disease, stroke); (3) diabetes mellitus; (4) severe infection, autoimmune disease, malignancy, or hematologic disorders; (5) recent use of thiazide diuretics, steroids, or urate-lowering agents; (6) history of thyroid dysfunction; (7) thyroid-affecting medications within the past six months (amiodarone, iodine preparations, phenytoin); and (8) pregnancy. All participants provided informed consent, and the study was approved by the Medical Ethics Committee of Xianyang Hospital of Yan' an University (Approval No.: YDXY-KY-2021-011).

Data Collection General Information: We collected demographic data including sex, age, occupation, education level, smoking and alcohol consumption history, and medication use. Body mass index (BMI) was calculated from height and weight measurements. Blood pressure was measured twice in the right upper limb using a desktop sphygmomanometer, and the average value was recorded.

Laboratory Measurements: Fasting blood samples collected the morning after admission were analyzed for total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), and SUA using an automatic biochemical analyzer (Hitachi, Japan). Thyroid hormones including TSH, FT3, and FT4 were measured using an e601 electrochemiluminescence immunoassay analyzer (Roche, Germany).

Diagnostic Criteria: Essential hypertension was diagnosed according to the *Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revision)* [13]: non-consecutive three blood pressure measurements showing systolic blood pressure (SBP) $ $140 mmHg and/or diastolic blood pressure (DBP) $ $90 mmHg; or 24-hour ambulatory blood pressure monitoring showing average BP $ $130/80 mmHg, daytime $ $135/85 mmHg, or nighttime $ $120/70 mmHg; or previously diagnosed hypertension with regular antihypertensive medication use. HUA was defined as SUA >420 mol/L in males and >360 mol/L in females [14]. Normal thyroid function was defined as TSH 0.27–4.20 IU/ml, FT3 3.1–6.8 pmol/L, and FT4 12.0–22.0 pmol/L.

Statistical Analysis Data were analyzed using SPSS 26.0 software. Normally distributed continuous variables are presented as mean ± standard deviation (x±s) and compared using independent samples t-tests. Non-normally distributed variables are expressed as median (interquartile range) [M(QR)] and compared using Mann-Whitney U tests. Categorical variables are presented as percentages and compared using ^{2} tests. Multivariate logistic regression analysis was performed to identify factors influencing HUA development in EH

patients. Pearson correlation analysis assessed relationships between thyroid hormone levels and SUA. Statistical significance was set at $P<0.05$.

Results

Comparison of Baseline Characteristics and Biochemical Parameters A total of 267 euthyroid EH patients were enrolled, including 166 in the non-HUA group (72 males, 94 females) and 101 in the HUA group (63 males, 38 females). No significant differences were observed between groups in SBP or HDL-C levels ($P>0.05$). However, the HUA group showed significantly higher proportions of male patients, BMI, DBP, smoking and alcohol consumption rates, TC, TG, LDL-C, and Scr levels, while age was significantly lower ($P<0.05$) .

Comparison of SUA and Thyroid Hormone Levels SUA and FT3 levels were significantly higher in the HUA group compared to the non-HUA group ($P<0.05$), while TSH and FT4 levels showed no significant differences between groups ($P>0.05$) .

Multivariate Logistic Regression Analysis of HUA Risk Factors Using HUA status as the dependent variable and statistically significant indicators from Tables 1 and 2 (sex, age, BMI, DBP, smoking status, alcohol consumption, TC, TG, LDL-C, FT3, Scr) as independent variables , multivariate logistic regression analysis identified male sex, elevated BMI, FT3, TG, LDL-C, Scr levels, and younger age as independent risk factors for HUA in EH patients ($P<0.05$). Notably, each standard deviation increase in FT3 level increased HUA risk by 1.297-fold (OR=2.297, 95% CI: 1.326–3.977) .

Correlation Between FT3 and SUA Levels Pearson correlation analysis revealed a positive correlation between FT3 and SUA levels in EH patients ($r=0.327$, $P<0.001$) [Figure 1: see original paper].

Discussion

Growing evidence links HUA to adverse cardiovascular events including EH, with elevated SUA identified as an independent risk factor for hypertension [15]. One study reported that HUA had the strongest association with EH risk among middle-aged and elderly populations, showing no significant impact on diabetes, heart disease, or stroke risk after adjusting for confounders [16], highlighting the close relationship between SUA and EH. However, factors contributing to HUA in EH patients remain controversial. While thyroid dysfunction has been implicated in HUA pathogenesis [8], with both hyperthyroidism and hypothyroidism associated with elevated SUA [9,10], the relationship between thyroid hormone levels within the normal range and HUA risk in EH patients has not been well characterized.

Our retrospective analysis demonstrated significantly higher FT3 levels in the HUA group compared to the non-HUA group. Multivariate logistic regression revealed that elevated FT3 was positively associated with HUA risk, independent of TSH and FT4 levels. Pearson correlation analysis confirmed an independent positive correlation between FT3 and SUA. These findings align with a 2019 study of 48,526 healthy individuals showing significant differences in TSH, FT3, and FT4 across SUA levels, with SUA correlating linearly with FT3 and FT4 but not TSH [20]. Similarly, Wang et al. reported an independent positive correlation between FT3 and SUA in 1,186 euthyroid individuals [21]. Our results support these observations, though larger sample sizes are needed for further validation.

The mechanism by which FT3 influences HUA development remains unclear. We initially hypothesized involvement of reduced estimated glomerular filtration rate (eGFR), but evidence suggests otherwise. One study of 2,180 euthyroid subjects found FT3 levels independently positively correlated with eGFR [22], while another study of 10,589 euthyroid individuals found no significant association between FT3 and eGFR [23]. These inconsistent findings suggest that elevated FT3 does not impair UA excretion through reduced eGFR. Instead, as UA is the end product of purine metabolism, FT3 may accelerate purine catabolism, increasing endogenous UA production [24]. Recent research indicates that FT3 can influence hepatic urate production by binding to thyroid hormone receptors and promoting Period-2 transcription, thereby affecting nucleotide metabolic enzyme activity and increasing urate generation [25]. Therefore, the mechanism linking FT3 to HUA may involve enhanced UA production rather than impaired excretion.

Beyond FT3, our study identified elevated BMI, TG, and LDL-C as HUA risk factors, consistent with previous research [26]. A recent study identified TG as an independent HUA risk factor associated with elevated SUA [27]. As the kidneys are the primary organs for UA excretion, renal dysfunction reduces UA clearance and increases SUA levels. Scr, a key indicator of renal function, correlates closely with HUA [28]. Interestingly, we found younger age to be a HUA risk factor, contrary to previous reports. This discrepancy may be attributed to the higher proportion of male HUA patients in our cohort, as males develop HUA at a younger age than females. Previous studies have reported higher HUA incidence in males, with peak onset at 40–49 years compared to postmenopausal age (48–55 years) in females [29].

Conclusion

In euthyroid EH patients, elevated FT3 levels represent a risk factor for HUA development, while FT4 and TSH show no significant association with HUA. This cross-sectional study with a small sample size cannot establish causality between FT3 and HUA. Additionally, our hospitalized cohort with older average age may not represent all EH patients, particularly newly diagnosed cases. Given the limited research on thyroid hormone levels and HUA risk in EH pa-

tients, larger prospective studies are needed to clarify the clinical significance of thyroid hormones in EH patients with HUA.

Author Contributions: ZHAO Wei conceived and designed the study, analyzed and interpreted results, and drafted the manuscript. YANG Shanshan and TANG Rongjie collected data. SUN Feng organized data and performed statistical analysis. LIAN Qiufang revised the manuscript. YANG Fang was responsible for quality control and review. LIAN Qiufang provided overall supervision.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.