Correlation of Serum FT4 with Serum Uric Acid and Comparison of Uric Acid in Subjects with and without Atrial Fibrillation in Graves' Disease: A Cross-Sectional Study

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ABSTRACT

Background: *Cardiovascular diseases increase the mortality risk in Graves' disease (GD) patients. Atrial fibrillation (AF) is one of the most prevalent cardiovascular diseases in GD. Hyperthyroidism that occurs in GD may increase uric acid levels, while uric acid levels can also increase the risk of AF in the general population. This study is designed to observe the correlation between free T4 (FT4) and uric acid, and compare of uric acid in subjects with and without AF in GD.* ***Methods:*** *A cross-sectional study was conducted, including GD patients who met research criteria in Dr. Cipto Mangunkusumo Hospital during 2024. We performed history taking, physical examination, laboratory examination, and electrocardiogram for each subject. Data was analyzed using Pearson or Spearman correlation, and bivariate analysis to evaluate the comparison of uric acid in subjects with and without AF.* ***Results:*** *We included 74 subjects, with an average age was 41 years, mostly female (86.5%), and 62.2% had normal FT4 levels. AF occurred only in 4.1% subjects. Mean of uric acid is 4.71 ± 1.2 mg/dl, which is within the normal range. No correlation was found between FT4 and uric acid (r = 0.076; p = 0.520), including after adjustment with subgroup analysis based on thyroid status, gender, and diabetes mellitus. Mean of uric acid is not statistically different between subjects with and without AF (4.9 ± 1.01 mg/dl vs 4.7 ± 1.2 mg/dl; p = 0.785).* ***Conclusion:*** *No significant correlation was found between FT4 and uric acid. Mean of uric acid is not statistically different between subjects with and without AF.*

Keywords*: atrial fibrillation, free T4, Graves' disease, uric acid.*

INTRODUCTION

Graves' disease (GD) is a chronic autoimmune disease marked by autoantibodies against thyroid thyroid-stimulating hormone (TSH) receptor. This antibody causes dysregulation of thyroid hormone production and secretion, and then hyperthyroidism occurs. Hyperthyroidism takes place in 1.2-1.6% worldwide.[1] In Indonesia, hyperthyroidism prevalence is 0.4%[2], and GD prevalence is 21% of all thyroid dysfunction in Dr. Cipto Mangunkusumo National Hospital.[3] Although GD is rare, GD increases morbidity and mortality related to its manifestation, including thyrotoxicosis, Graves' ophthalmopathy (GO), increased risk of thromboembolism, and cardiovascular disease (CVD).[1,4,5] Cardiovascular disease is one of the main causes of mortality in GD.[6] One of the most prevalent CVDs in GD is atrial fibrillation (AF), with a prevalence that ranges from 10-60%, while in hyperthyroidism, AF prevalence ranges from 5-15%.[7,8]

Graves' disease also increases blood uric acid levels through hyperthyroidism. A high level of FT4 induces increased purine metabolism.[9] In GD, uric acid was found to be associated with active GO, with a sensitivity of 94.3% and specificity of 85.2%.[10] It is related to the increased accumulation of orbital adipose tissue in GO patients.[11] Several reports have studied the association between thyroid status and uric acid, reporting conflicting results.[12–17] Research studies related to the correlation between free T4 (FT4) and uric acid also reported conflicting results.[18–23] Helmy et al reported that there is a moderate correlation between FT4 and uric acid ($r = 0.482$; $p = 0.007$) in subjects with hyperthyroidism,[18] while Vishwanath et al reported that there is no correlation between uric acid and FT4, FT3, and thyroid-stimulating hormone (TSH) in patients with hyperthyroid, hypothyroid, and euthyroid states.[19] A study on the correlation between FT4 and uric acid has not been performed in Indonesia, and also has not been performed before, especially on subjects with GD.

In GD, higher level of FT4, male gender, and older age is reported to be associated with early onset of AF, while chronic obstructive pulmonary disease (COPD), older age, and heart failure are reported to be associated with late onset of AF. Atrial fibrillation increases mortality in GD patients (HR 16.32; 95% CI 4.66-56.58).[20] Besides hyperthyroidism, uric acid is also associated with increased risk of AF in the general population.[24–27] High uric acid leads to inflammation, apoptosis, hypertension, metabolic syndrome, reactive oxygen species (ROS) formation pathway, thus it causes structural and functional heart remodelling and induces cardiac electrophysiology impairment.[28] In this study, we aim to observe the correlation between FT4 and uric acid, and also compare of uric acid in subjects with and without AF in GD patients. We hope to find other modifiable nontraditional risk factors, which as uric acid, to prevent AF in GD patients.

METHODS

A cross-sectional study was performed in the Department of Internal Medicine, Dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia, from January to December 2024.

Study Participants

We included adult GD patients at the metabolic-endocrinology outpatient clinic, Dr. Cipto Mangunkusumo National Hospital. The minimum sample size required for this study was 68 subjects, with a power of 90% and a 95% level of confidence. Study participants were chosen consecutively. Each subject had to sign the informed consent form to be included in this study. Subjects with chronic kidney disease, malignancy, tumor lysis syndrome, critically ill condition, alcohol consumption, drugs that could interfere with uric acid level consumption (xanthine oxidase, uricosuric, pegloticase, diuretic, aspirin, pyrazinamide, ethambutol, cytotoxic agent, cyclosporin, tacrolimus, and nicotinic acid), and pregnant women were excluded.

Patients Assessment

Participants who met study criteria were included, and then they provided written informed consent. All participants underwent an interview, physical and laboratory examination, and electrocardiogram (ECG). The interview was performed at first admission, included sociodemographic, clinical condition,

comorbidities, drug consumption, and whether the patient had a history of radioactive iodine (RAI) and/or thyroidectomy. At the second admission, physical examination (blood pressure, body weight, and height), laboratory examination (uric acid, FT4, and HbA1c), and ECG were performed.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) v.29. Characteristics of subjects will be presented as percentages for categorical data and mean (standard deviation) or median (min-max) for continuous data. Pearson or Spearman correlation was used to observe the correlation between FT4 and uric acid. Comparison of the uric acid level in subjects with and without AF was observed using an unpaired t-test. The results were considered statistically significant if the p-value < 0.05.

Ethical Consideration and Approval

The protocol of this study has been approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (KET-821/UN2.F1/ETIK/PPM.00.02/2024). All participants provided written informed consent before participation.

RESULTS

Seventy-seven subjects were recruited in this study, yet one subject got sick and had to be admitted to another hospital, and 2 subjects did not come to the second admission. At the end of this study, we included 74 participants (**Figure 1**).

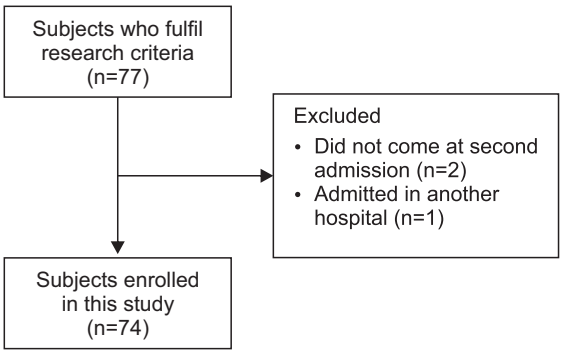

Figure 1. Flow chart of patient recruitment

Sociodemographic and Clinical Characteristics

In this study, the mean age is 41 years old and predominantly female (86.5%). Most of the participants had normal FT4 levels (62.2%), with a median of FT4 is 1.04 ng/dl and TSH is 0.55 μIU/ml. We observed only 4.1% participants with AF. Mean of uric acid is also within normal limit (4.71 ± 1.2 ng/dl). Sociodemographic and clinical characteristics of this study are reported in **Table 1**.

Correlation between FT4 and Uric Acid in Graves' Disease

From Spearman correlation, we inferred that there is no correlation between FT4 and uric acid in GD patients, even after adjustment by subgroup analysis based on thyroid status, gender, and diabetes mellitus status (**Table 2**). A scattered plot of correlation between FT4 and uric acid in Graves' disease was presented in **Figure 2**.

Table 1. Sociodemographic and clinical characteristics of subjects (n = 74)

Sociodemographic and Clinical Characteristics	Total (n = 74)
Age (years)*	41.34 ± 13.04
Productive age	67 (90.5%)
Elderly	7 (9.5%)
Gender	
Female	64 (86.5%)
Male	10 (13.5%)
Smoking history	6 (8.1%)
Body mass index (kg/m^2)*	23.63 ± 4.68
Underweight	10 (13.5%)
Normal BMI	28 (37.8%)
Overweight	9 (12.2%)
Obese	27 (36.5%)
Diabetes mellitus	4 (5.4%)
Dyslipidemia	23 (31.1%)
Hypertension	20 (27%)
Serum FT4 (ng/dl)**	1.04 (0.4-5)
Serum TSHs (μIU/ml)**	0.55 (0.001-27.42)
Thyroid status	
Normal FT4 level	46 (62.2%)
Low FT4 level	16 (21.6%)
High FT4 level	12 (16.2%)
Serum uric acid (mg/dl)*	4.71 ± 1.2
Atrial fibrillation	3 (4.1%)

Data are presented in percentage for categorical variables (%), *Data are presented in mean (standard deviation), **Data are presented in median (min-max)
FT4: free T4, n: number of subjects, TSHs: thyroid-stimulating hormone

Table 2. Correlation between FT4 and uric acid in Graves' disease (n = 74)

Subgroup	Classification	Uric Acid	
		r	p value
Total subjects		0.076	0.520
Thyroid status	Normal FT4 level	0.186	0.216
	Low FT4 level	0.169	0.532
	High FT4 level	-0.111	0.731
Gender	Male	0.593	0.071
	Female	0.031	0.810
Diabetes mellitus status	No diabetes mellitus	0.139	0.252
	Diabetes mellitus	-0.405	0.595

Spearman's rho test, r = correlation coefficient

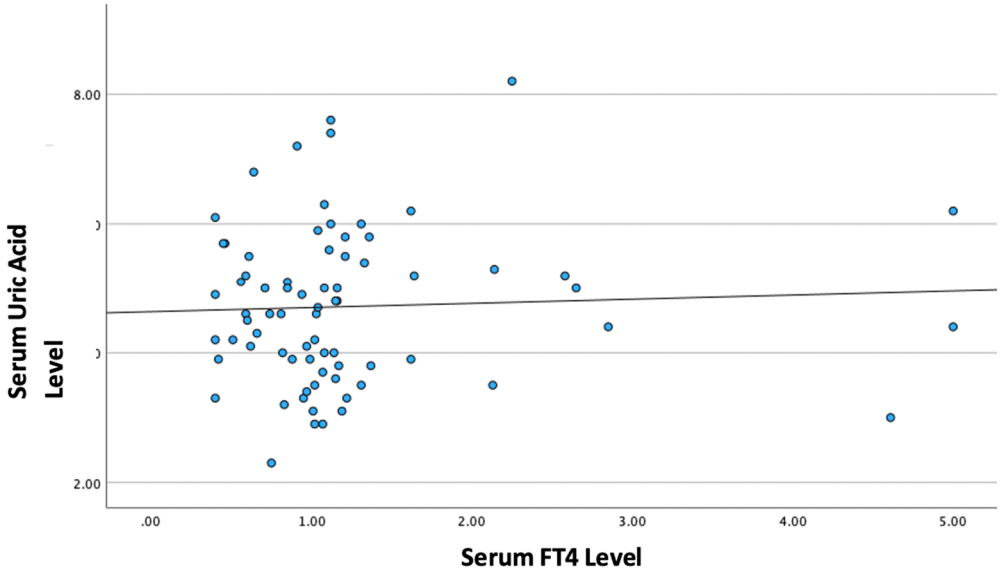

Figure 2. Scattered plot of correlation between FT4 and uric acid in Graves' disease

Table 3. Comparison of uric acid in subjects with and without atrial fibrillation in Graves' disease

Variable	Classification		p value
	With Atrial Fibrillation	Without Atrial Fibrillation	
Uric acid (mg/dl)	4.9 ± 1.01	4.7 ± 1.2	0.785

Unpaired T-test

Comparison of Uric Acid in Subjects with and Without Atrial Fibrillation in Graves's Disease

From this study, we observed that the mean of uric acid is higher in subjects with AF compared to subjects without AF, yet this comparison is not statistically different (**Table 3**).

DISCUSSION

Graves' disease occurs more in females, 86.5% with a mean age of 41 years. This result is similar to reports from the European Thyroid Association and other studies, which claim that most of the GD patients are female, with a ratio of 6 : 1 and a range of ages is 30-60 years.[1,12,18] This study involves 62.2% subjects with normal FT4 levels and only 16.2% subjects with high FT4 levels; thus, we also find that the prevalence of AF is very low (4.1%). It is lower than other study, which declares that the prevalence of AF in hyperthyroid patients ranges from 5-15%[7], and the prevalence of AF in GF patients ranges from 10-60%.[8] In this study, we

observe that subjects with normal body mass index (BMI) is 37.8% and the prevalence of obesity is 36.5%, which may be due to a lower prevalence of hyperthyroid. This study involves GD subjects regardless of thyroid status, as most of the patients in Dr. Cipto Mangunkusumo Hospital already get antithyroid drugs (ATD) and some of them already undergo definitive treatment, such as radioactive iodine (RAI) and thyroidectomy.

High FT4 level leads to increased uric acid by accelerating purine metabolism.[18,19] Uric acid excretion is also increased in high FT4 levels, yet this mechanism is not as fast as purine metabolism, so hyperuricemia still occurs.[12] In this study, we observed no statistically significant correlation between FT4 and uric acid in GD patients ($r = 0.076$; $p = 0.52$), even after we performed subgroup analysis based on thyroid status, gender, and diabetes mellitus status. This result is different from Helmy et al, who report a moderate correlation between FT4 and uric acid level ($r = 0.54$; $p = 0.007$) in hyperthyroid subjects.[18] The difference between this study and Helmy et al is due to most of the subjects in this study already having normal FT4 levels. Our study result is supported by Vishwanath et al and Torkian et al. Both studies reported that there is no correlation between FT4 and uric acid, even in patients with hypothyroid, hyperthyroid, and euthyroid status.[19,23] Zhang et al study reports that there is a weak correlation between uric FT3 and FT4 with uric acid in both male and female genders, yet the male gender is associated with a higher prevalence of hyperuricemia.[29] A Different result is observed because in this study, most of the subjects are female (86.5%).

We find an interesting theory that there is also a correlation between FT4 and uric acid in hypothyroid subjects from other studies.[20–22] Hypothyroid status is related to increased uric acid because of decreased glomerular filtration rate (GFR) and renal blood flow (RBF)[19,20] through several mechanisms, including an increase in insulin growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), leads to vasoconstriction of renal blood vessels; alteration of glomerular structure associates with limitation of glomerular filtration area; decreased cardiomyocyte activity causes decreased cardiac output; and decreased renal ion transporter leads to increased Na^+ and Cl^- concentration.[30,31] Decreased GFR in hypothyroid patients is supported by Naguib et al study, which reports increased GFR before and after therapy in hypothyroid subjects (67 ± 11 ml/min/1.73 m^2 vs 79 ± 13 ml/min/1.73 m^2).[31] Studies related to the correlation between FT4 and uric acid in subjects with thyroid dysfunction were presented in **Table 4.**

In this study, we observe mean of uric acid is higher in subjects with AF compared to those without AF, yet this result is not statistically significant (4.9 ± 1.01 mg/dl vs 4.7 ± 1.2 mg/dl; $p = 0.785$). This result is different from other meta-analysis studies that are performed in the general population.[24–27] Our study is performed with a cross-sectional design; most of the subjects are female, of productive age, have normal FT4 levels, and we did not classify AF in this study. Naser et al report that hyperthyroid status, male gender, and elderly age are associated with early onset of AF, while older age is associated with late onset of AF.[8]

This is the first study in Indonesia to observe the correlation between FT4 and uric acid, and a comparison of uric acid in subjects with and without AF in GD patients. We also perform subgroup analysis based on thyroid status, gender, and diabetes mellitus status. Previous studies were performed in the normal population or with thyroid dysfunction, but did not mention GD as the cause of thyroid dysfunction. Our study also has several limitations. First, this study uses a cross-sectional design, which is not suitable for observing the comparison of uric acid in subjects with and without AF due to the low prevalence of AF in GD patients. Second, this study involves predominantly subjects with normal FT4 levels. Further study evaluating the correlation between FT4 and uric acid in subjects with high FT4 levels, and also case control, nested case control, or multi-centre cohort study to evaluate comparison of uric acid in subjects with and without AF in GD patients is warranted.

Table 4. Studies related to the correlation between FT4 and uric acid in subjects with thyroid dysfunction

Study	Type	Country	Subjects	Results
Vishwanath HL, 2019[19]	Case control	India	Hyperthyroid (n = 25) Hypothyroid (n = 25) Euthyroid (n = 35)	There was no correlation between uric acid and FT4 in subjects with euthyroid (r = -0.02), hypothyroid (r = -0.25), and hyperthyroid (r = -0.01).
Helmy MY, 2020[18]	Case control	Egypt	Hyperthyroid (n = 35) Hypothyroid (n = 35) Normal (n = 35)	There was a moderate correlation between uric acid and FT4 in hyperthyroid subjects (r = 0.482; p = 0.007), while there was no correlation between uric acid and FT4 in hypothyroid subjects (r = -0.185; p = 0.326).
Torkian P, 2020[23]	Case control	Iran	Subclinical hypothyroid (n = 118) Euthyroid (n = 121)	No correlation was found between uric acid and T4 in subjects with subclinical hypothyroid (r = 0.020; p = 0.83) and euthyroid (r -0.044; p = 0.63).
Noureen F, 2020[20]	Cross sectional	Pakistan	Overt hypothyroid (n = 38) Subclinical hypothyroid (n = 38) Healthy subjects (n = 38)	No correlation was found between uric acid and FT4 in subjects with overt hypothyroid (r = -0.124; p = 0.442), subclinical hypothyroid (r = -0.119; p = 0.476), and healthy subjects (r = 0.151; p = 0.364).
Akagunduz B, 2021[21]	Cross sectional	Turkey	Overt hypothyroid (n = 81) Subclinical hypothyroid (n = 118) Healthy subjects (n = 203)	There was weak inverse correlation between uric acid and FT4 in all subjects (r = -0.244; p < 0.001), while in subgroup analysis no correlation was found between uric acid and FT4 in overt hypothyroidism (r = 0.032; p = 0.778), subclinical hypothyroidism (r = 0.042; p = 0.647), and healthy subjects (r = 0.059; p = 0.402).
Eranhikkal H, 2023[22]	Cross sectional	India	Hypothyroid (n = 70) Healthy subjects (n = 121)	No correlation was found between uric acid and FT4 in subjects with hypothyroidism (r = -0.018; p = 0.883).
Zhang J, 2016[29]	Cross sectional	China	Subject with unknown thyroid dysfunction Male (n = 6870) Female (n = 4576)	Weak correlation was found between uric acid and FT4 in male and female subjects (r = 0.042; p < 0.01 and r = 0.073; p < 0.01).

CONCLUSION

We concluded that there is no correlation between FT4 and uric acid in GD patients. In this study, we also observed that there is no statistically significant comparison of uric acid in subjects with and without AF in GD patients, yet the effect of the small prevalence of AF in this study must be taken into account.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

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