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Original Article

Correlation between Thyroid Stimulating Hormone and Renal Function in Euthyroid Residents of Japan: Results from the Kyushu and Okinawa Population Study (KOPS)

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***Aim*: The present large-scale Japanese population study was performed to evaluate the relation between the serum thyroid stimulating hormone (TSH) level and renal function.**
***Methods*: Out of 1,374 residents who participated in a free public physical examination between 2010 and 2011, we evaluated the data of 888 participants for whom the serum TSH level and estimated glomerular filtration rate (eGFR) were successfully measured. The participants were categorized into three groups based on TSH levels (normal TSH, ≤2.4; high-normal TSH, 2.5−4.4; and subclinical hypothyroid, ≥4.5 μIU/mL). Multiple linear regression analysis adjusted for cardiovascular risk factors was performed to determine the relationship between serum TSH level and renal function.**
***Results*: The mean±SD TSH level was 2.0±1.4 μIU/mL, and 75.9% (n=674) of the participants had normal, 17.9% (n=159) had high-normal, and 6.2% (n=55) had subclinical hypothyroid TSH levels. The mean eGFR significantly decreased with increased TSH levels (normal TSH, 79.3±14.1; high-normal TSH, 77.4±13.0; and subclinical hypothyroid, 72.3±12.2 mL/min/1.73 m^2: P for trend <0.01). Multiple linear regression analysis extracted log-transformed TSH level as an independent factor correlated with eGFR in the high-normal TSH group (beta=−0.18, P=0.02).**
***Conclusions*: Our findings demonstrated a significant correlation between serum TSH levels and eGFR in high-normal TSH participants. In healthy individuals, high-normal TSH levels indicate increased the risk of chronic kidney disease.**

Key words: Thyroid stimulating hormone, Chronic kidney disease, Atherosclerosis

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Introduction

Hypothyroidism is a common endocrine disorder that is a potent risk factor for cardiovascular disease and chronic kidney disease (CKD)[1, 2]. Previous studies reported that hypothyroidism can be caused by mechanisms such as decreased cardiac output[3], increased vascular resistance[4], and elevated serum creatinine levels caused by myopathy or rhabdomyolysis[5]. Subclinical hypothyroidism, expressed as serum thyroid stimulating hormone (TSH) elevation despite normal serum thyroid hormone levels, has also been associated with cardiovascular disease[6] and CKD[7]. Moreover, within the normal range, serum TSH levels per se have been shown to be associated with these disorders[8-10]. The correlation of thyroid dysfunction with cardiovascular disease and CKD has been well established. The prevalence of subclinical hypothyroidism is 4%−10% in the general population[11]. For the management of subclinical hypothyroidism, repeated evaluation of thyroid function and treatment with thyroid hormone replacement therapy have been reported to be effective[12, 13].

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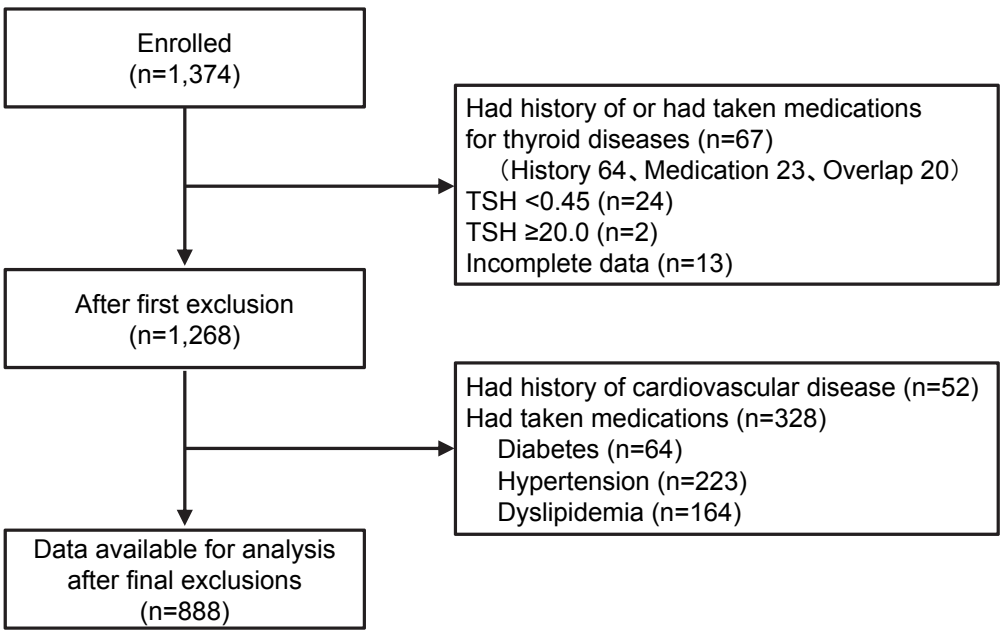

Fig. 1. Flowchart depicting participant eligibility
TSH: thyroid stimulating hormone

However, the best course of management for such patients remains to be elucidated because of the high prevalence of this disorder.

Moreover, hypothyroidism is reported to be associated with carotid atherosclerosis[14, 15], which may be a potent risk factor for CKD[16]. Few studies have evaluated the impact of carotid atherosclerosis on the relationship between hypothyroidism and renal dysfunction. Carotid arterial intima-media thickness (IMT) is a commonly used marker of atherosclerosis, and it is a strong predictor of atherosclerotic disease[17].

Based on the above, we assessed the relationship between serum TSH levels and renal function in a healthy Japanese population. In addition, we examined whether or not the association is correlated with atherosclerosis.

Methods

Study Subjects

The Kyushu and Okinawa Population Study (KOPS) was first conducted between 2010 and 2011 as a survey of the incidence of vascular events associated with lifestyle-related diseases[16, 18-21]. In this sub-study we evaluated the data of the residents of Kasuya Town, which is a suburban area adjacent to Fukuoka City, with a population of approximately 45,000 residents. The participants were residents, who notified by means of a local newspaper and public announcements, about a free annual health examination to be conducted by our department. Of 1,374 residents aged ≥20 who participated in the physical examination, 486 were excluded, including residents who had a history of thyroid disease or who had received medication for thyroid disease ($n=67$). Other exclusion criteria included overt hyperthyroidism (TSH <0.45 μIU/mL, $n=24$); overt hypothyroidism (TSH ≥20.0 μIU/mL, $n=2$); self-reported history of cardiovascular disease ($n=52$); medication for diabetes, hypertension, or dyslipidemia ($n=328$); and incomplete laboratory data ($n=13$), rendering the data of 888 healthy residents (351 men and 537 women; aged 39−84 years, mean ± SD: 56.6 ± 9.1 years) available for the final analysis (**Fig. 1**). The participants were classified into three groups based on TSH levels: normal TSH ≤2.4 μIU/mL; high-normal TSH 2.5−4.4 μIU/mL TSH; and subclinical hypothyroid TSH ≥4.5 μIU/mL groups[22].

The study design was approved by the Kyushu University Hospital Ethics Committee (permission number: 590-00), and written informed consent was obtained from each participant prior to the examination. The study was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000.

Anthropometric Measurement and Questionnaire

Anthropometric measurements were acquired with each subject wearing indoor clothing and no shoes. Body mass index was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured on the right arm, in the sitting position, with an auto-

mated sphygmomanometer (HEM-780, Omron Healthcare, Kyoto, Japan) after 5 min of rest[23]. Each participant completed a self-administrated questionnaire that included smoking status, alcohol consumption, medical history, and use of drugs. The questionnaire was evaluated for incomplete or inconsistent answers, first by nurses and again by our staff physicians.

Laboratory Measurements

Blood samples were collected at baseline and follow-up after an overnight fast of at least 8 h. Plasma/serum samples after separation were stored at 4℃ in refrigerated containers and sent to a commercial laboratory (SRL, Fukuoka, Japan). Plasma glucose concentration was measured using the hexokinase-glucose-6-phosphate dehydrogenase method. The HbA1c level was measured by immunoassay of fresh whole blood samples. At baseline, the serum levels of creatinine, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined enzymatically, and low density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula[24]. The CLIA immunoassay was used to measure serum TSH levels. eGFR was calculated using the Modification of Diet in Renal Disease study equation, modified for Japanese subjects: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL)$^{-1.094}$ × Age$^{-0.287}$ (× 0.739 for females)[25].

Ultrasonographic Measurement

Carotid IMT was assessed using ultrasound. Participants were supine with slight hyperextension and the neck rotated in the direction opposite to the probe. Carotid artery lesions were measured using high resolution B-mode ultrasonography with a 7.5 MHz linear array probe (UF-4300R, Fukuda Denshi Co., Ltd, Tokyo, Japan) by competent physicians of our department. Images were obtained 20 mm proximal to the origin of the carotid bulb at the far wall by the Intimascope IMT measurement software (Media Cross Co., Ltd, Tokyo, Japan)[26]. The mean value of the bilateral average of the common carotid artery was used as the carotid mean-IMT level.

Statistical Analysis

Data are presented as the mean ± standard deviation or percentage. Because TSH levels were distributed in a skewed manner, they were log-transformed before statistical analysis. Correlations between eGFR and various variables are presented as the *Pearson*'s correlation coefficient and those between eGFR and categorical variables are presented as the *Spearman*'s correlation coefficient. Analysis of variance, chi-square test, and trend test were used to evaluate differences between categories based on TSH levels. Multiple linear regression analysis to evaluate the association between eGFR and other parameters was adjusted for age, sex, and carotid IMT in Model 1 and additionally adjusted for current smoking, body mass index, HbA1c, and LDL-cholesterol in Model 2. In addition, analyses were performed with the participants categorized on the basis of TSH levels. Statistical analysis was performed using SPSS ver.22.0 (SPSS Inc., IBM, Somers, NY). $P < 0.05$ was considered to be statistically significant.

Results

Clinical Characteristics

Of the participants, 75.9% ($n = 674$) had normal, 17.9% ($n = 159$) had high-normal, and 6.2% ($n = 55$) had subclinical hypothyroid TSH levels. The mean ± SD TSH level was 2.0 ± 1.4 μIU/mL, and eGFR < 60 mL/min/1.73 m^2 was noted in 6.9% of the participants. The mean eGFR was 78.5 ± 14.0 mL/min/1.73 m^2.

Clinical characteristics classified on the basis of sex and TSH levels are shown in **Table 1** and **Table 2**, respectively. The proportion females and age significantly increased with each group. The percentage of current smokers was significantly different among the groups. Body mass index, blood pressure, fasting plasma glucose, HbA1c, HDL-cholesterol, LDL-cholesterol, triglycerides, and carotid IMT were not significantly different among the groups. The mean eGFR significantly decreased with each group, and the trend test for the three TSH level categories showed statistical significance (P for trend < 0.01) (**Fig. 2**).

Correlations between TSH and eGFR

The mean eGFR was 78.5 ± 14.0 mL/min/1.73 m^2, and it significantly decreased with age ($r = -0.30$, $P < 0.01$), log-transformed TSH ($r = -0.15$, $P < 0.01$), and carotid IMT ($r = -0.11$, $P < 0.01$). The correlation between log-transformed TSH and carotid IMT was not statistically significant ($P = 0.96$). Furthermore, eGFR did not show a significant correlation with carotid IMT ($P = 0.61$). Multiple linear regression analysis adjusted for the significant covariates (sex and carotid IMT) extracted age (beta = −0.29, $P < 0.01$) and log-transformed TSH (beta = −0.11, $P < 0.01$) as independent factors associated with eGFR. When the cardiovascular risk factors (body mass index, current smoking, HbA1c, and LDL-cholesterol) were forced into the model, the correlation of log-transformed TSH with eGFR remained significant (beta = −0.11, $P < 0.01$) (**Table 3**).

When categorized on the basis of TSH level, the correlation between log-transformed TSH and eGFR

Table 1. Clinical characteristics by sex

Variables	All (n=888)	Men (n=351)	Women (n=537)	P value*
Serum TSH (μIU/mL)	2.0±1.4	1.9±1.3	2.2±1.4	<0.01
Age (years)	56.6±9.1	56.9±9.5	56.4±8.9	0.46
Body mass index (kg/m^2)	22.1±3.1	23.0±2.9	21.5±3.0	<0.01
Habitual drinking (%)	46.5	66.0	33.5	<0.01
Current smoking (%)	17.1	27.6	10.1	<0.01
Systolic blood pressure (mmHg)	117.4±16.2	120.5±16.8	115.0±15.4	<0.01
Diastolic blood pressure (mmHg)	70.6±11.5	73.2±11.8	68.5±11.0	<0.01
Fasting plasma glucose (mmol/L)	5.12±0.78	5.30±0.95	5.00±0.61	<0.01
HbA1c (%)	5.47±0.47	5.53±0.57	5.43±0.39	<0.01
LDL-cholesterol (mmol/L)	3.33±0.82	3.30±0.84	3.35±0.80	0.37
HDL-cholesterol (mmol/L)	1.73±0.43	1.56±0.4	1.85±0.42	<0.01
Triglycerides (mmol/L)	1.19±0.86	1.46±1.14	1.01±0.54	<0.01
Carotid intima-media thickness (mm)	0.58±0.10	0.60±0.11	0.56±0.09	<0.01
eGFR (mL/min/1.73 m^2)	78.5±14.0	78.2±15.0	78.7±13.1	0.57

Data are presented as the mean±standard deviation or number of subjects (%) for categorical variables. *P values for analysis of men and women. Overall P values were calculated by analysis of variance or chi-square test. TSH: thyroid stimulating hormone, eGFR: estimated glomerular filtration rate.

Table 2. Clinical characteristics classified by serum TSH level

Variables	TSH level classification			P value*
	Normal TSH (n=674)	High-normal TSH (n=159)	Subclinical hypothyroid (n=55)	
Serum TSH (μIU/mL)	1.4±0.5	3.2±0.5	6.1±1.5	<0.001
Age (years)	56.1±9.4	57.3±8.2	60.1±7.0	<0.001
Women (%)	57.3	69.8	72.7	<0.01
Body mass index (kg/m^2)	22.1±3.1	22.3±3.2	22.1±2.7	0.80
Habitual drinking (%)	48.0	41.7	41.8	0.28
Current smoking (%)	19.7	8.0	10.9	<0.01
Systolic blood pressure (mmHg)	117.2±15.7	117.4±17.8	119.9±18.5	0.61
Diastolic blood pressure (mmHg)	70.7±11.8	70.5±11.1	69.6±9.9	0.85
Fasting plasma glucose (mmol/L)	5.13±0.78	5.08±0.71	5.06±1.0	0.72
HbA1c (%)	5.5±0.5	5.5±0.5	5.4±0.4	0.77
LDL-cholesterol (mmol/L)	3.30±0.82	3.43±0.87	3.39±0.62	0.19
HDL-cholesterol (mmol/L)	1.73±0.42	1.74±0.48	1.77±0.40	0.76
Triglycerides (mmol/L)	1.19±0.89	1.19±0.81	1.15±0.64	0.95
Carotid intima-media thickness (mm)	0.57±0.10	0.57±0.10	0.59±0.12	0.56

Data are presented as the mean±standard deviation or number of subjects (%) for categorical variables. *P values for analysis of each group. Overall P values were calculated by analysis of variance or chi-square test. TSH: thyroid stimulating hormone.

was significant in the normal TSH (r=−0.08, P=0.03) and high-normal TSH groups (r=−0.18, P=0.03), but not in the subclinical hypothyroid group (r=−0.04, P=0.76). In the multiple linear regression analysis adjusted for the covariates age, sex, and carotid IMT, significant correlation of log-transformed TSH with eGFR was found only in the high-normal TSH group (beta=−0.19, P=0.02). In addition, after adjusting for the cardiovascular risk factors, body mass index, current smoking, HbA1c, and LDL-cholesterol, the correlation between log-transformed TSH and eGFR remained significant (beta=−0.18, P=0.02) (**Table 3**).

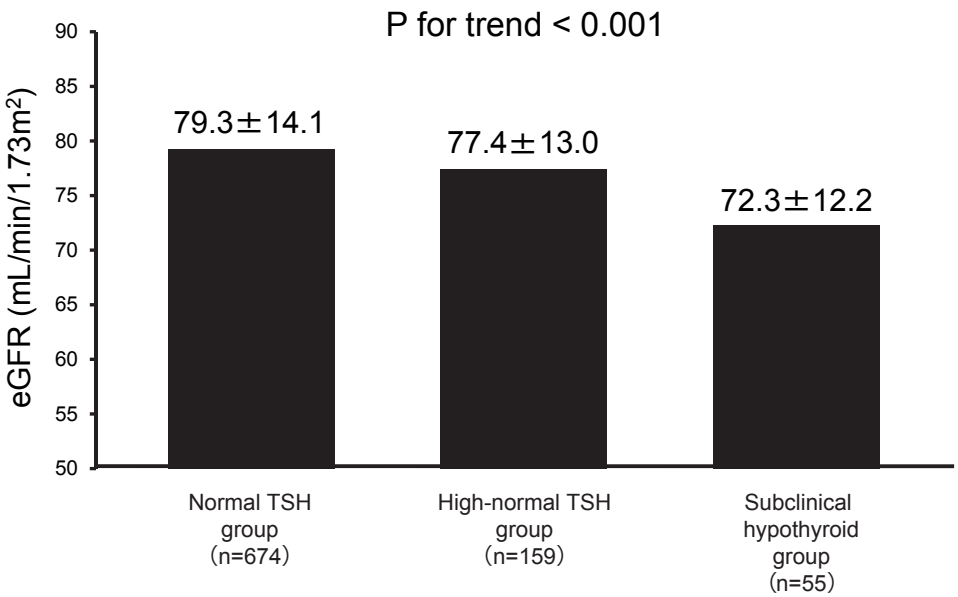

Fig. 2. Trend test for correlation between serum TSH levels and eGFR as per TSH level categories

Data are presented as the mean ± standard deviation. *P* for trend was calculated by the trend test.
TSH: thyroid stimulating hormone, eGFR: estimated glomerular filtration rate

Evaluation Classified by Sex

In addition to the above evaluations, we performed a subgroup analysis in which the participants were categorized on the basis of sex. The clinical characteristics are presented in **Table 1**. For women, multiple linear regression analysis adjusted for the significant covariate carotid IMT extracted age (beta = −0.27, $P < 0.01$) and log-transformed TSH (beta = −0.14, $P < 0.01$) as independent factors associated with eGFR. When the cardiovascular risk factors, body mass index, current smoking, HbA1c, and LDL-cholesterol were forced into the model, the correlation of log-transformed TSH with eGFR remained significant (beta = −0.14, $P < 0.01$) (**Table 4A**). In contrast, for men, the multiple linear regression analysis adjusted for the covariate age and carotid IMT showed that log-transformed TSH was not significantly associated with eGFR (beta = −0.08, $P = 0.14$) (**Table 4B**). The above indicates that sex had little influence on the analysis.

Trend Test with Participants Classified by Age

We stratified the participants into two groups based on age (younger or older than 60 years) and performed a trend test to evaluate renal function as per TSH levels. Although no statistical significance (*P* for trend = 0.06) was observed in the reduction of eGFR based on TSH category for the younger group, the analysis for the older group showed significance differences (*P* for trend = 0.04).

Discussion

The main finding of the present study is that significant correlation of elevated serum TSH levels with renal dysfunction was limited to participants with a high-normal TSH levels. Moreover, this association was independent from effect of carotid atherosclerosis. To the best of our knowledge, few studies have attempted to evaluate such a large, healthy population for identifying an independent association between serum TSH levels and renal function.

We found a significant, independent correlation between serum TSH levels and eGFR for the entire study population and for the high-normal TSH group. In the subclinical hypothyroidism group, the correlation between log-transformed TSH and eGFR was not significant, which may be related to the lower number of subjects in this group. In addition, eGFR significantly decreased with increasing TSH levels (**Fig. 2**). Previous studies have shown a significant correlation between elevated serum TSH levels and renal dysfunction in patients with hypothyroidism[27] or subclinical hypothyroidism[7]. Furthermore, Zhang, *et al.*[9] reported that a higher TSH level within the normal range was independently associated with the incidence of CKD and that the association was progressive until it plateaued at approximately 3.0 IU/mL TSH. Although the mean age of the participants in the present study was higher than that in the study by Zhang *et al.* (56.6

Table 3. Multiple linear regression analysis for the association between eGFR and serum TSH level

	Model 1		Model 2	
	beta	*P* value	beta	*P* value
All participants (*n* = 888)				
Log-transformed TSH (μIU/mL)	−0.11	<0.01	−0.11	<0.01
Carotid intima-media thickness (mm)	0.03	0.46	0.03	0.49
Normal TSH group (*n* = 674)				
Log-transformed TSH (μIU/mL)	−0.06	0.12	−0.06	0.12
Carotid intima-media thickness (mm)	0.018	0.68	0.02	0.70
High-normal TSH group (*n* = 159)				
Log-transformed TSH (μIU/mL)	−0.19	0.02	−0.18	0.02
Carotid intima-media thickness (mm)	0.06	0.47	0.06	0.49
Subclinical hypothyroid group (*n* = 55)				
Log-transformed TSH (μIU/mL)	−0.06	0.67	−0.01	0.93
Carotid intima-media thickness (mm)	0.06	0.72	0.19	0.20

Beta coefficient and *P* value were calculated by multiple linear regression analysis.
Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex, body mass index, current smoking, HbA1c, and LDL-cholesterol
TSH: thyroid stimulating hormone, eGFR: estimated glomerular filtration rate.

vs. 38.0 years), our finding of a significant correlation between serum TSH levels and eGFR in the high-normal TSH group (TSH 2.5−4.4 μIU/mL) was similar. This indicates that, regardless of age, the correlation between elevated serum TSH levels and renal dysfunction may commence at a serum TSH level of 2.5−3.0 μIU/mL.

We found that carotid IMT was not significantly correlated with eGFR and that the significant correlation between the serum TSH level and eGFR was independent of carotid atherosclerosis. In our previous study, higher carotid IMT was independently associated with the development of CKD, whereas carotid IMT was not significantly correlated with the presence of CKD in the baseline analysis[16]. Thus, the significant cross-sectional correlation between carotid IMT and eGFR would not be significant in relatively healthy individuals without overt atherosclerosis. Furthermore, the findings of the present study indicate that hypothyroidism contributes to the development of CKD through a mechanism other than atherosclerosis. Decreased renal blood flow from low cardiac output[3], elevated systemic vascular resistance[4], or muscle metabolism disorders[5] have been proposed as potential mechanisms.

There was no significant association between serum TSH levels and carotid IMT in the present study. The results of previous studies that have evaluated this association are controversial, and the degree of hypothyroidism of study participants may be a factor. In fact, a positive correlation between serum TSH levels and carotid IMT of patients with subclinical hypothyroidism was reported[14]. In contrast, this correlation was not significant among euthyroid subjects[28]. Further research will be necessary to investigate the correlation of hypothyroidism with atherosclerotic diseases other than CKD, such as evaluation of the correlation in subgroups stratified on the basis of TSH level.

As described in **Table 1**, several variables, including serum TSH levels and carotid IMT, were different for men and women, which indicates that sex may have influenced the results of this study. However, the correlation remained significant in multiple linear regression analysis adjusted for covariates, including sex, which was performed to evaluate the correlation between serum TSH levels and eGFR (**Table 3**). In addition, we found no significant, independent correlation between serum TSH levels and sex or eGFR and sex. Subgroup analysis stratified on the basis of sex was difficult for several reasons, including a low number of participants to evaluate interaction[29]. Because of the above, sex would seem to have had little influence on the results of this study.

We performed a trend test to evaluate renal function categorized on the basis of TSH levels and participants stratified on the basis of age because we considered that the results for the entire cohort may simply reflect a decrease in renal function with increasing age. The results of the evaluation of eGFR reduction as per TSH level category showed statistical significance only in the older group. However, although there were fewer participants, the result for the younger group was near significance. It is suggested that statistical significance of the trend test for the entire subjects might

Table 4A. Multiple linear regression analysis of the association between the eGFR and serum TSH level of women

	Model 1		Model 2	
	beta	*P* value	beta	*P* value
Analyzed data (*n* = 537)				
Log-transformed TSH (μIU/mL)	−0.14	<0.01	−0.14	<0.01
Carotid intima-media thickness (mm)	0.04	0.43	0.04	0.39
Normal TSH (*n* = 386)				
Log-transformed TSH (μIU/mL)	−0.03	0.56	−0.04	0.43
Carotid intima-media thickness (mm)	0.04	0.50	0.04	0.51
High-normal TSH (*n* = 111)				
Log-transformed TSH (μIU/mL)	−0.19	0.04	−0.21	0.03
Carotid intima-media thickness (mm)	0.04	0.69	0.04	0.71
Subclinical hypothyroid (*n* = 40)				
Log-transformed TSH (μIU/mL)	0.03	0.86	0.02	0.87
Carotid intima-media thickness (mm)	0.07	0.69	0.28	0.07

Beta coefficient and *P* value were calculated by multiple linear regression analysis.
Model 1: Adjusted for age.
Model 2: Adjusted for age, body mass index, current smoking, HbA1c, and LDL-cholesterol.
TSH: thyroid stimulating hormone, eGFR: estimated glomerular filtration rate

Table 4B. Multiple linear regression analysis of the association between the eGFR and serum TSH level of men

	Model 1		Model 2	
	beta	*P* value	beta	*P* value
Analyzed data (*n* = 351)				
Log-transformed TSH (μIU/mL)	−0.08	0.14	−0.07	0.20
Carotid intima-media thickness (mm)	0.02	0.79	0.02	0.76
Normal TSH (*n* = 288)				
Log-transformed TSH (μIU/mL)	−0.09	0.13	−0.08	0.21
Carotid intima-media thickness (mm)	−0.002	0.97	−0.005	0.93
High-normal TSH (*n* = 48)				
Log-transformed TSH (μIU/mL)	−0.17	0.25	−0.09	0.57
Carotid intima-media thickness (mm)	0.12	0.48	0.20	0.23
Subclinical hypothyroid (*n* = 15)				
Log-transformed TSH (μIU/mL)	−0.36	0.27	−0.23	0.72
Carotid intima-media thickness (mm)	0.09	0.78	0.66	0.41

Beta coefficient and *P* value were calculated by multiple linear regression analysis.
Model 1: Adjusted for age.
Model 2: Adjusted for age, body mass index, current smoking, HbA1c, and LDL-cholesterol.
TSH: thyroid stimulating hormone, eGFR: estimated glomerular filtration rate

not just a reflection of a decrease of renal function with increasing age.

The present study had several limitations. First, a cause-effect association cannot be inferred from our cross-sectional study. Second, classification into the TSH levels was based on a single examination, which could have false positive or false negative results that could lead to misclassification. Third, subclinical hypothyroidism is biochemically defined as the concentration of normal free thyroxin (FT4) in the presence of elevated TSH levels; therefore, it would have been better to measure FT4. However, primary hypothyroidism is much more frequent than secondary hypothyroidism in both sexes at all ages[30], and the TSH level, but not FT4, has been associated with renal prognosis[9]. In addition, the prevalence of overt hypothyroidism is far less (0.4%) than the prevalence of subclinical hypothyroidism (9.0%)[31]; thus, evaluation without the mea-

surement of FT4 should be sufficient. Fourth, we did not investigate proteinuria, an alternative marker of chronic kidney disease. Finally, data regarding possible confounding factors such as volume overload or cardiac function[32, 33] were not collected; only healthy residents were analyzed in this study. Despite the above limitations, our findings will contribute to the management of mild thyroid dysfunction for the prevention of CKD in healthy individuals.

Conclusion

We found that eGFR gradually decreased with elevated serum TSH levels and that the significant linear correlation between serum TSH levels and eGFR was limited to participants with a high-normal TSH levels. Moreover, this association was not attributable to carotid IMT. Further research is needed to investigate whether or not aggressive management, including repeated evaluation for thyroid and renal function or thyroid hormone replacement therapy for persons with mild TSH elevation, can improve renal prognosis.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Research design: Y Tanaka, N Furusyo

Data analysis: Y Tanaka, N Furusyo

Collection and assembly of data: Y Tanaka, H Ikezaki, Y Kato, T Ueyama, S Yamasaki, M Masayuki

Wrote or contributed to the writing of the manuscript: Y Tanaka, N Furusyo, J Hayashi

Final approval of the article: Y Tanaka, N Furusyo

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