Research Article

Relationship between Thyroid and Kidney Function: Analysis from the Korea National Health and Nutrition Examination Survey Between 2013 and 2015

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Abstract

Introduction: Thyroid function is evaluated by thyroid stimulating hormone (TSH) and free thyroxine (fT4). Although many studies have indicated an intimate relationship between thyroid hormones and kidney functions, reports about the simultaneous evaluation of TSH and fT4 are rare. ***Objective:*** We aimed to analyze the association between TSH and kidney function, with emphasis on a potential nonlinear relationship, and identify an independent relationship between fT4 and kidney function. ***Methods:*** We reviewed the data of 7,061 subjects in the Korea National Health and Nutrition Examination Surveys who were randomly subsampled for thyroid function evaluation between 2013 and 2015. A total of 5,578 subjects were included in the final analysis, after excluding people <18 years old, and those with a short fasting time, abnormal fT4 levels, and thyroid disease or related medications. Creatinine-based estimated glomerular filtration rate (eGFR) was used to define kidney function. ***Results:*** A 1 mmol/L increase of logarithmic TSH was associated with decreased eGFR (β: –1.8; 95% CI –2.3 to –1.2; $p < 0.001$), according to multivariate linear regression analysis. On the multivariate generalized additive model plot, TSH demonstrated an L-shaped relationship with eGFR, showing a steeper slope for 0–4 mIU/L of TSH. A 1 μg/dL increase of fT4 was also associated with decreased eGFR (β: –7.0; 95% CI –0.94 to –4.7; $p < 0.001$) on the multivariate linear regression analysis; this association was reversed after adjusting for age. On the mediation analysis, the indirect effect via age and direct effect per 1 μg/dL increase of fT4 on eGFR was 9.9 (8.1 to 11.7, $p < 0.001$) and –7.1 (–9.3 to –4.8, $p < 0.001$), respectively. ***Conclusions:*** Increased TSH was associated with decreased eGFR, particularly in the reference range. The direct effect of increased fT4 was decreased eGFR, which may be affected indirectly by age.

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Introduction

Thyroid hormones affect many aspects of the kidney, including development and hemodynamics [1]. Thyroid dysfunctions should be properly and promptly treated due to the effects of thyroid hormones on the body metabolism [2, 3]. Subclinical hypothyroidism (SCH) is common disease and thyroid dysfunction; there is still controversy regarding over- and undertreatment of this disease [4]. SCH is defined when the thyroid stimulating hormone (TSH) level is increased and the free thyroxine (fT4) level is normal [5]. In routine practice, doctors and clinicians do not recommend treating nonsymptomatic SCH [6]. This may be because the TSH levels in about 60% of SCH patients with a mild elevation in TSH (4–10 mIU/L) become normalized without intervention [7].

Nonetheless, SCH can progress to overt hypothyroidism, especially when the TSH level ≥10 mIU/L [8]. Furthermore, it may be associated with diastolic heart dysfunction [9], arterial stiffness [10], diastolic hypertension [11], dyslipidemia [12], and insulin resistance [13], which ultimately increase the risk of heart failure [14, 15], cardiovascular (CV) disease, and mortality [16, 17]. Furthermore, SCH may also have a negative effect on kidney health. Experimental studies have suggested that a deficiency in thyroid hormones may reduce the glomerular filtration rate [18] by reducing cardiac output, renal plasma flow, and sodium resorption [19]. To date, many studies have suggested that SCH was associated with reduced kidney function [20–24]. Some have even reported that an elevated TSH level, but within the reference range, was associated with chronic kidney disease (CKD) [25–27].

However, there are few studies that have examined the effects of TSH and fT4 on kidney function simultaneously [25, 28–30]. In fact, the metabolism of T4 is altered in CKD patients; deiodination of T4 and T4-binding plasma proteins is reduced and inhibitors of T4 binding to plasma proteins and metabolic acidosis are presented [19]. Therefore, we postulated that the simultaneous evaluation of TSH and fT4 is important, particularly for evaluating kidney function. In this study, we aimed to analyze the association between TSH and kidney function, with emphasis on a potentially nonlinear relationship, and identify an independent relationship between fT4 and kidney function, using data from the Korea National Health and Nutrition Examination Survey (KNHANES), a nationwide government-administered survey. We hypothesize that high TSH and fT4 level could affect kidney function decline.

Material and Methods

Participants

The KNHANES has been conducted periodically, since 1998, to assess the health and nutritional status of the civilian, noninstitutionalized population of Korea. Participants are selected using multistage, stratified probability sampling. This study used data from the KNHANES from 2013 to 2015. Of 29,321 candidates, 22,948 people agreed to participate (participation rate: 78.3%). For the 22,948 subjects, thyroid function tests were performed by subsampling 2,400 subjects aged ≥10 years in each survey; a total of 7,061 subjects underwent thyroid function tests during the KNHANES, from 2013 to 2015. We excluded 897 participants who were <18 years old. Of the 6,164 adult participants, 127 with an overnight fasting time <8 h, 168 with a low fT4 level (<0.92 μg/dL), 193 with a high fT4 level (≥1.60 μg/dL), 86 with a physician diagnosis of thyroid disease or cancer, and 12 who were administered thyroid medications were also excluded. Therefore, we included 5,578 subjects for the final analysis.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki, and full approval of the study was obtained from the Institutional Review Board (IRB) of the Korea Centers for Disease Control (IRB 2013-07CON-03-4C, 2013-12EXP-03-5C, 2015-01-02-6C). All data were fully anonymized before we accessed them. All KNHANES participants provided written informed consent to have their data used in research.

Thyroid Function Test

Thyroid function was tested using serum levels of fT4, TSH, and antithyroid peroxidase antibodies (anti-TPO Abs). Serum levels of fT4, TSH, and anti-TPO Abs were measured by an electro-chemiluminescence immunoassay (Cobas: Roche Diagnostics, Penzberg, Germany). Thyroid status was defined according to a general clinical consensus [31–34]. Subjects were diagnosed with hyperthyroidism if they had a TSH level ≤0.1 mIU/L, euthyroidism if they had a TSH level ranging from 0.1 to 4.0 mIU/L, and hypothyroidism if they had a TSH level ≥4.0 mIU/L. Anti-TPO Abs levels ≥34 IU/mL were assumed to be positive [35].

Measurements

A standardized interview was conducted in the homes of the subjects to determine disease diagnosis. Blood pressure (BP) was measured 3 times using a standard mercury sphygmomanometer (Baumanometer Wall Unit 33 [0850]; Baum Co., Inc., Copiague, NY, USA). Participants did not smoke, sat down for at least 5 min, and measured BP at heart level. The average of the 3 measures was used. Body mass index was calculated by dividing the weight by the square of the height (kg/m^2). Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the highest point of the iliac crest, using a tape measure (Seca 200, Seca, Germany), to the nearest 0.1 cm. Blood and urine samples were collected in the morning after >8 h fasting and analyzed in a central laboratory (Neodin Medical Institute, Seoul, Korea). High-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and fasting glucose (FG) levels were measured using the Hitachi 7600 Automatic Analyzer (Hitachi, Japan). Hemoglobin levels were measured using the Sodium Lauryl Sulfate hemoglobin detection method [36]. White blood cell counts were measured using flow cytometry with a semiconductor laser. The XE-2100D (2013–2014, Sysmex, Japan) and XN-9000 (2015, Sysmex, Japan) were used to measure hemoglobin and white blood cells counts. Urine iodine was measured with inductively coupled plasma-mass spectroscopy using Perkinelmer inductively coupled plasma-mass spectroscopy (Perkin Elmer, Waltham, MA, USA), while urine protein was measured with a dipstick method using the UriSys 2400 analyzer (Roche, Germany). Serum creatinine levels were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) with the Jaffe method [37], and kidney function was calculated from the serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation [38].

Definitions

Metabolic disorders were defined following the recommendations of the International Diabetes Federation [39]. Central obesity was defined as a WC ≥90 cm for men and WC ≥80 cm for women. Raised BP was defined as systolic BP ≥130 mm Hg, diastolic BP ≥85 mm Hg, or treatment with antihypertensive drugs. Raised FG was defined as FG ≥100 mg/dL, treatment with insulin or oral antidiabetic drugs, or a previous diagnosis of type 2 diabetes. Raised TG was defined as TG ≥150 mg/dL. Reduced HDL-C level was defined as HDL-C <40 mg/dL for men and HDL-C <50 mg/dL for women or administration of specific treatments for dyslipidemia. Previous CV disease was defined by a diagnosis of stroke, myocardial infarction, or angina. Liver disease was defined by a previous diagnosis of the hepatitis B or C virus or

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liver cirrhosis. Proteinuria was defined as a protein level of 1+ or higher on the dipstick urinalysis. Regular exercise was defined as doing strenuous exercise (i.e., soccer, climbing) > 3 days a week. Regular walking was defined as walking for >10 min for travel, such as commuting or shopping, >3 days a week. High income was defined by the highest quartile of monthly personal income. Alcohol consumption was defined by consuming alcohol more than once a month within the last year.

Statistical Analyses

Histograms and Q-Q plots were constructed to evaluate the normality of continuous variables. Normally distributed continuous variables were expressed as mean (SD), while nonnormally distributed continuous variables were expressed as median (interquartile range). Categorical variables were expressed as number (percentage). The *p* trend was analyzed for normally distributed continuous variables using a one-way analysis of variance. For nonnormally distributed continuous variables, the Jonckheere-Terpstra test was used. The Cochran-Armitage test was used for categorical variables. The Locally Weighted Scatter-plot Smoother (LOWESS) was used to evaluate the simple relationship between TSH, fT4, and estimated glomerular filtration rate (eGFR). Linear regression analysis was performed to analyze the relationship between the thyroid function and eGFR. A multivariate generalized additive model (GAM) for Gaussian distributions was used to analyze the nonlinear relationship between the TSH and the eGFR, using the "mgcv" package in R developed by R Core Team. For the model fitting, Akaike information criterion, which indicates the more suitable model with a lower score, was calculated. Mediation analysis among fT4 and eGFR was performed using the "mediation" package. The treatment was fT4, the mediator was age, the outcome was eGFR, and the pretreatment covariates were age, sex, systolic and diastolic BP, TG, FG, HDL-C, body mass index, WC, hemoglobin, white blood cells, urine iodine, proteinuria, cancer, previous CV disease, liver disease, regular exercise and walking, and the status of income, education, smoking, alcohol consumption, and mental stress, with 2,000 times simulation. Using mediation analysis, average causal mediation effects, average direct effects, and total effects were calculated. A *p* value <0.05 was considered statistically significant. All analyses were performed using R version 3.6.0 (R core Team 2019; R foundation for Statistical Computing, Vienna, Austria).

Results

The mean age of the 5,578 participants was 43.9 years and 49.5% were men. The percentages of participants with raised BP, raised FG, raised TG, reduced HDL-C, and central obesity were 25.0, 30.6, 28.9, 31.7, and 32.1%, respectively. Median TSH, mean fT4, and percentage of positive anti-TPO Abs were 2.2 mIU/L, 1.2 μg/dL, and 6.6%, respectively. The mean eGFR was 99.9 mL/min/1.73 m^2, and the percentage of subjects with proteinuria was 0.9%.

The baseline characteristics of the study population, according to TSH quartiles, are shown in Table 1. Although age (*p* = 0.745) was not associated with the TSH quartiles, the proportion of men (*p* < 0.001) decreased as the TSH quartile increased. The percentages of alcohol consumption (*p* = 0.011), current smoking (*p* < 0.001), and high mental stress (*p* = 0.001) decreased, as the TSH quartile increased, while the percentage of high income (*p* = 0.005) increased. The percentage of raised FG (*p* = 0.022) decreased, while percentages of reduced HDL-C (*p* = 0.005) and central obesity (*p* = 0.011) increased as the TSH quartile increased. As the TSH quartile increased, fT4 (*p* < 0.001) decreased, while urine iodine (*p* < 0.001) and the percentage of positive anti-TPO Abs (*p* < 0.001) increased. With the increase of the TSH quartile, eGFR (*p* < 0.001) decreased. Proteinuria (*p* = 0.491) was not associated

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Table 1. Clinical characteristics of the study population according to TSH quartile groups

	TSH quartile groups (n = 5,578)				p trend
	<1.53 mIU/L (n = 1,390)	1.53–2.23 mIU/L (n = 1,383)	2.23–3.24 mIU/L (n = 1,401)	>3.24 mIU/L (n = 1,404)	
Age, years	43.9±14.9	43.5±15.0	44.1±15.2	44.1±15.5	0.745
Men	772 [55.5]	714 [51.6]	699 [49.9]*	576 [41.0]*†‡	<0.001
College graduate	457 [35.1]	477 [37.2]	479 [37.2]	471 [36.2]	0.596
High income	284 [20.6]	317 [22.8]	358 [25.7]*	343 [24.5]*	0.005
Alcohol consumption	830 [62.2]	796 [60.2]	789 [58.9]	776 [57.5]*	0.011
Current smoking	420 [32.1]	319 [24.6]*	281 [21.4]*	184 [14.0]*†‡	<0.001
High mental stress	379 [28.4]	382 [28.9]	337 [25.2]†	320 [23.8]*†	0.001
Regular exercise	166 [12.7]	152 [11.9]	153 [11.9]	171 [13.2]	0.749
Regular walking	888 [68.3]	859 [67.1]	877 [68.1]	888 [68.4]	0.818
Raised BP	340 [24.6]	333 [24.1]	363 [26.0]	359 [25.7]	0.327
Raised FG	452 [33.6]	430 [32.4]	423 [31.6]	400 [29.5]*	0.022
Raised TG	389 [28.0]	384 [27.8]	422 [30.1]	416 [29.6]	0.180
Reduced HDL-C	431 [31.0]	394 [28.5]	455 [32.5]†	489 [34.8]*†	0.005
Central obesity	412 [29.7]	438 [31.7]	467 [33.4]*	475 [33.9]*	0.011
Cancer	22 [1.7]	29 [2.3]	29 [2.2]	28 [2.1]	0.444
Liver disease	16 [1.2]	16 [1.2]	27 [2.1]	21 [1.6]	0.196
Previous CVD	29 [2.2]	36 [2.8]	41 [3.2]	35 [2.7]	0.391
Systolic BP, mm Hg	116.3±16.0	115.9±15.4	117.1±15.8	116.5±16.2	0.259
Diastolic BP, mm Hg	75.2±10.2	75.4±9.9	75.6±10.2	75.5±10.2	0.731
BMI, kg/m²	23.8±3.6	23.7±3.5	23.9±3.5	23.8±3.8	0.809
WC, cm	81.2±10.2	81.0±10.2	81.4±10.2	80.6±10.7	0.173
FG, mmol/L	5.2 (4.9–5.7)	5.2 (4.9–5.7)	5.2 (4.9–5.6)	5.2 (4.9–5.6)*	0.020
TG, mmol/L	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.2 (0.8–1.9)	1.2 (0.8–1.8)*	0.025
HDL-C, mmol/L	1.3±0.3	1.3±0.3	1.3±0.3	1.3±0.3	0.772
eGFR, mL/min/1.73 m²	100.0±15.8	99.4±16.4	97.6±16.2*†	98.4±16.8*	<0.001
TSH, mIU/L	1.2 (0.9–1.3)	1.9 (1.7–2.0)*	2.7 (2.4–2.9)*†	4.3 (3.7–5.4)*†‡	<0.001
Free T4, µg/dL	1.3±0.15	1.3±0.15	1.2±0.15*†	1.2±0.15*†‡	<0.001
Positive anti-TPO-Abs	57 [4.1]	60 [4.3]	85 [6.1]*†	165 [11.8]*†‡	<0.001
Hemoglobin, g/dL	14.4±1.6	14.3±1.6	14.3±1.6	14.1±1.5*†‡	<0.001
WBC, ×10³/µL	6.5±1.8	6.3±1.7*	6.3±1.6*	6.3±1.7	0.005
Urine iodine, µg/L	244 (136.0–542.8)	259 (138.0–563.8)	276 (157.0–647.5)*†	378 (182.0–898.0)*†‡	<0.001
Proteinuria	12 [0.9]	15 [1.2]	14 [1.1]	9 [0.7]	0.491

Values are expressed as mean ± SD for normally distributed continuous variables, median ± interquartile range for nonnormally distributed continuous variables, and percentage for categorical variables. p trend was analyzed for normally distributed continuous variables by ANOVA, for nonnormally distributed continuous variables by Jonckheere-Terpstra tests, and for categorical variables by Cochran-Armitage test for trend. *, †, and ‡ meant p < 0.05 when compared to <1.51 mmol/L, 1.51–2.23 mmol/L, 2.23–3.28 mmol/L groups of thyroid stimulating hormone, respectively, using Bonferroni post hoc analysis of one-way ANOVA for normally distributed continuous variables, Mann-Whitney U tests for nonnormally distributed continuous variables, and chi-square tests for categorical variables. TSH, thyroid stimulating hormone; BP, blood pressure; FG, fasting glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular disease; BMI, body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate; T4, thyroxine; TPO-Ab, thyroid peroxidase antibody; WBC, white blood cells.

Table 2. The effect of thyroid function on kidney function

	Univariate		Model 1		Model 2	
	beta (95% CI)	*p* value	beta (95% CI)	*p* value	beta (95% CI)	*p* value
TPO-Ab (yes vs. no)	–3.8 (–5.5 to –2.1)	<0.001	–2.5 (–4.2 to –0.9)		–0.8 (–2.1 to 0.5)	
Log-TSH, mmol/L	–1.5 (–2.2 to –0.8)	<0.001	–1.5 (–2.2 to –0.8)	<0.001	–1.8 (–2.3 to –1.2)	<0.001
Free T4, µg/dL	3.9 (1.1 to 6.8)	0.007	2.9 (0.0 to 5.9)	0.052	–7.0 (–9.4 to –4.7)	<0.001

In model 1, adjusted beta and 95% CI were calculated using multivariate linear regression analysis, entering all above variables with sex, systolic and diastolic blood pressure, triglyceride, fasting glucose, high-density lipoprotein cholesterol, body mass index, waist circumference, hemoglobin, urine iodine, white blood cells, proteinuria, cancer, previous cardiovascular disease, liver disease, regular exercise and walking, and the status of income, education, smoking, alcohol consumption, and mental stress status. In model 2, Adjusted beta and 95% CI were calculated by adding age to the variables used in model 1. TSH, thyroid stimulating hormone; T4, thyroxine; TPO-Ab, thyroid peroxidase antibody.
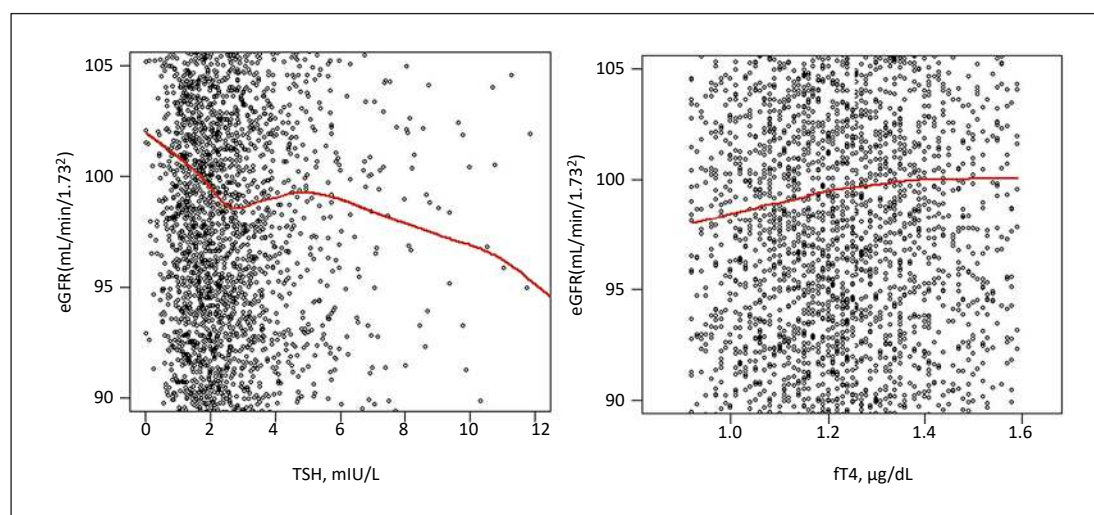

Fig. 1. Association between the TSH, fT4, and the eGFR. The red line indicated in the scatter plot is the LOWESS regression curve. All values were not transformed with either square root or logarithm. TSH, thyroid stimulation hormone; fT4, free thyroxine; eGFR, estimated glomerular filtration rate.

with the TSH quartile. White blood cell counts (*p* = 0.005) and the hemoglobin level (*p* < 0.001) significantly decreased as the TSH quartile increased.

The LOWESS regression curve revealed that an increase in TSH was associated with a steady decrease in the eGFR (Fig. 1). Multivariable linear regression analysis confirmed this inverse relationship between TSH and eGFR (Table 2). In the GAM plots (Fig. 2), we found that the inverse relationship between TSH and eGFR was particularly evident when plasma TSH was <4.0 mIU/L; however, there was no definite cut-point identified using Akaike information criterion analysis. This prominent inverse relationship was also found in subgroup analysis, which demonstrated that the statistical significance between TSH and eGFR was present only in the non-hypothyroid groups (Fig. 3). Furthermore, there were no significant effect modifiers, including the status of anti-TPO Abs, urine iodine, and eGFR.
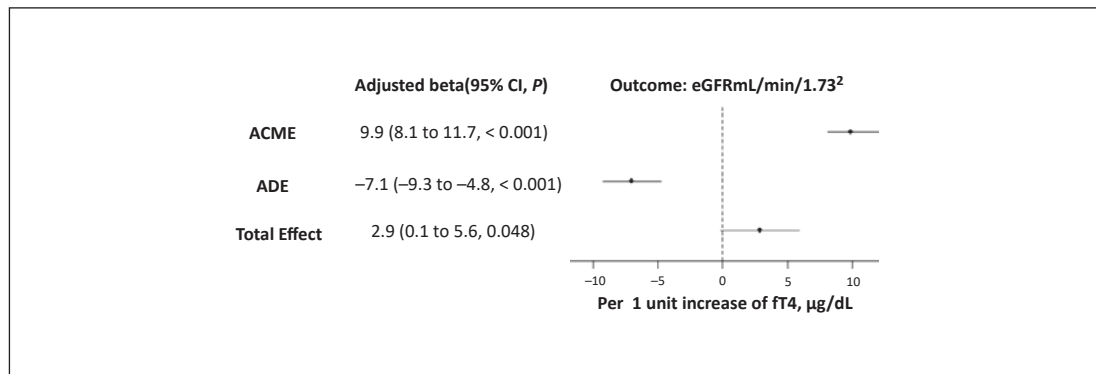
The LOWESS regression curve also revealed that an increase in fT4 was associated with an increase in the eGFR, plateauing in the higher fT4 range (Fig. 1). This positive relationship between fT4 and eGFR was confirmed in the univariate and multivariate linear regression
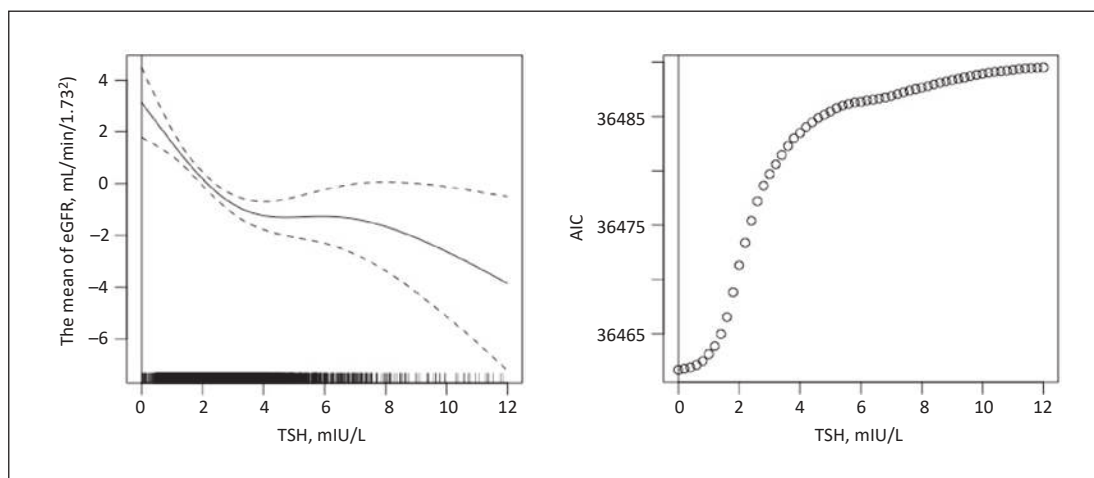
Fig. 2. GAM plot between TSH and eGFR. The dashed line indicate 95% CIs for value of the smoothed eGFR, using multivariate GAM analysis after adjusting for age, sex, systolic and diastolic BP, FG, TG, HDL-C, body mass index, WC, hemoglobin, urine iodine, white blood cells, proteinuria, cancer, previous CV disease, liver disease, regular exercise and walking, and the status of income, education, smoking, alcohol consumption, and mental stress. TSH, thyroid stimulating hormone; eGFR, estimated glomerular filtration rate; AIC, Akaike's information criterion.
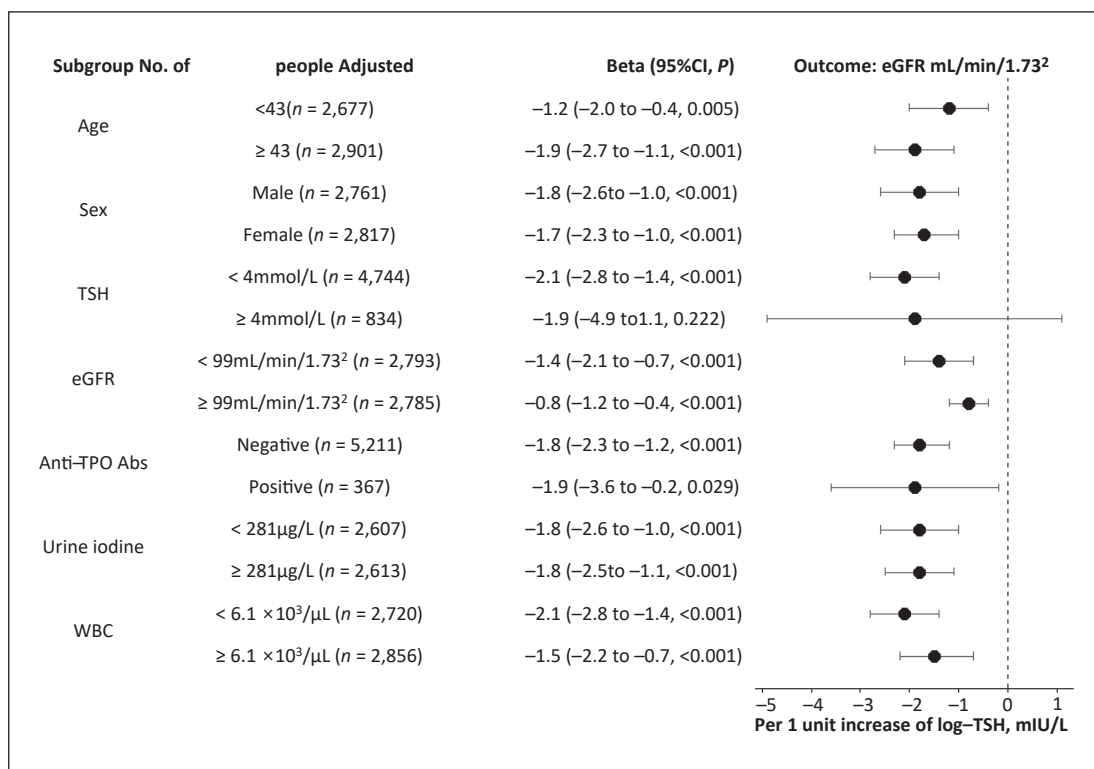

Fig. 3. Subgroup analysis for the relationship between the TSH and the eGFR. Adjusted beta and 95% CI were analyzed using multivariate linear regression analysis, entering into age, sex, systolic and diastolic BP, TG, FG, HDL-C, body mass index, WC, hemoglobin, white blood cells, urine iodine, proteinuria, cancer, previous CV disease, liver disease, regular exercise and walking, and the status of income, education, smoking, alcohol consumption, and mental stress status as covariates. TSH, thyroid stimulating hormone; eGFR, estimated glomerular filtration rate; WBC, white blood cells.

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Fig. 4. Mediation analysis among fT4, age, and the eGFR. Outcome was eGFR, treatment was TSH, mediator was age, and pre-treatment covariates were age, sex, systolic and diastolic BP, TG, FG, HDL-C, body mass index, WC, hemoglobin, white blood cells, urine iodine, proteinuria, cancer, previous CV disease, liver disease, regular exercise and walking, and the status of income, education, smoking, alcohol consumption, and mental stress status. Overall effects of treatment on outcome were adjusted by mediator and pretreatment covariates using multivariate linear regression analysis. Mediator was modeled by treatment and pretreatment covariates using multivariate linear regression analysis. eGFR, estimated glomerular filtration rate; ACME, average causal mediation effect; ADE, average direct effect; fT4, free thyroxine.

Fig. 5. The hypothesis of pathogenetic link between thyroid function and kidney function. TSH, thyroid stimulating hormone; fT4, free thyroxine; T3, triiodothyronine; TH, thyroid hormone; NTI, nonthyroidal illness; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
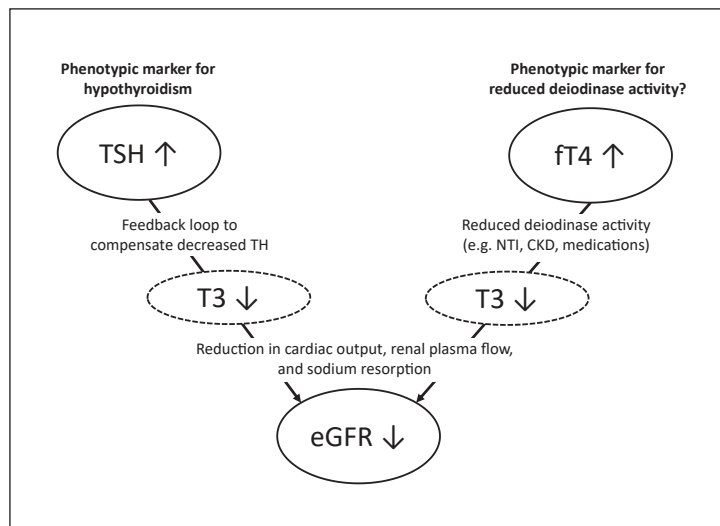
analyses (Model 1). However, adding age as covariate (Model 2) reversed the relationship between fT4 and eGFR (Table 2), suggesting a significant mediation effect by age. In mediation analysis (Fig. 4), increased fT4 was associated with increased eGFR indirectly when it was mediated by age. On the other hand, its direct effect on eGFR was negatively associated with eGFR. Finally, the total effect per 1 µg/dL increase of fT4 on eGFR was 2.9 (0.1–5.6, $p = 0.048$).

Discussion/Conclusions

SCH is common and about 15% of the elderly population may have SCH [40]. Despite its significant cardiometabolic hazards [11–17], treatment is only recommended when the TSH level is ≥10 mIU/L or if patients have significant symptoms [6]. However, kidney function is

not heavily considered when determining if treatment is necessary for SCH; however, numerous studies have revealed that SCH may cause a decline in kidney function [20–24, 30]. If small changes in the thyroid hormone levels, which are within the reference range, have negative effects on the kidney health, earlier replacement of thyroid hormone may prevent the progression of CKD in SCH patients [30]. Some studies have also reported that a higher TSH level within the reference range may also have renal hazards [25–27]; however, these studies did not evaluate a nonlinear relationship between TSH and eGFR. Although the metabolism of fT4 may be altered in CKD patients and a unique relationship between fT4 and eGFR may exist [19], an independent relationship between fT4 and eGFR has rarely been studied [25, 28, 29]. We simultaneously evaluated the impact of TSH and fT4 on eGFR, finding that TSH and eGFR showed an L-shaped relationship and demonstrated a significant association, particularly within the reference range of TSH. We also found that an increase in fT4 was directly associated with a decrease in eGFR, but was indirectly associated with increased eGFR via age.

In this study, we identified that an increased TSH was associated with decreased eGFR. These results were in accordance with previous studies. Chang et al. [20] reported that the OR and 95% CI of SCH for CKD was 1.74 (1.18–2.56) after analyzing 74,356 subjects from Taiwan. Toda et al. [23] also suggested that the ORs (95% CIs) of TSH 2.41–4.26 mIU/L and >4.26 mIU/L for CKD were 1.49 (1.33–1.67, $p < 0.001$) and 1.90 (1.57–2.30, $p < 0.001$), respectively, in 7,609 Japanese subjects. However, no known studies have investigated the nonlinear relationship between TSH and eGFR. In our GAM plots, we found that the relationship between TSH and eGFR was L-shaped, and the slope was steeper in the reference range for TSH (0–4 mIU/L). The subgroup analysis revealed that the renal hazard associated with increased TSH was only present in the non-hypothyroid groups. This may be because hypothyroidism is associated with increased age [41], bad habitual patterns [42, 43], lipotoxicity [44], and systemic inflammation [45], which may also attenuate thyroid hormone metabolism [46]. When considered with other studies that have reported an association between renal hazard and increased TSH, within the TSH reference range [22, 23, 25], our study results may suggest that a lower TSH level is associated with better kidney function. Therefore, future prospective studies need to be conducted to confirm the potential renoprotective effects of earlier thyroid hormone replacement.

We evaluated an independent relationship between fT4 and eGFR and identified that increased fT4 was associated with decreased eGFR. To our knowledge, there have been 4 studies that have reported an independent relationship between fT4 and kidney function. Zhang et al. [25] reported that fT4, within the reference range, was not associated with incident CKD development (mean age = 38.0 years). On the other hand, Huang et al. [28] suggested that increased fT4 was associated with an increased risk of incident CKD development (mean age = 59.3 years). Similarly, Anderson et al. [47] reported a negative relationship between fT4 and creatinine clearance in a study of 2,180 subjects from the general population with normal thyroid function (mean age = 47.3 years). Schultheiss et al. [29] also reported that increased fT4 was associated with an increased risk for reduced kidney function (mean age = 57.4 years). The differences in these results may partly be attributed to the age distribution of the participants; participants in 3 of the studies [28, 29, 47] were much older than those in the other study [25]. In our study, the mean age was 43.9 years.

We further analyzed the independent effect of fT4 on eGFR, with emphasis on the potential mediation effect of age. In multivariate linear regression analysis, adjusting for age reversed the relationship between fT4 and eGFR. In mediation analysis, the direct effect (not affected by age) of increased fT4, within the reference range, was decreased eGFR. Based on these results, we hypothesized that increased fT4, within the reference range, may signify hypothyroidism in the tissue level; this was the case with TSH (Fig. 5). This may be because T4 is a

prohormone and has to be converted into triiodothyronine (T3) via deiodination to act on nuclear thyroid hormone receptors [48]. Decreased conversion to T3 due to reduced deiodinase activity results in increased T4 levels [48]. Therefore, increased fT4 levels, which may be associated with conditions of reduced deiodinase activity (including nonthyroidal illness) [49], CKD [19], and medications including amiodarone [48], may have a negative impact on eGFR. The effect of age on the relationship between fT4 and eGFR, however, seemed to be more complex. In our mediation analysis, the indirect effect of increased fT4 levels, within the reference range, via age was to increase eGFR, although age is one of the known conditions to decrease deiodinase activity [50, 51]. At this point, further investigation is necessary to delineate if an age-related increase of fT4 levels, within the reference range, is associated with functional hyperthyroidism at the tissue level [1].

Our study has some limitations that should be addressed. First, this is a cross-sectional study, so it cannot ascertain the causal relationship. Therefore, follow-up cohort studies are needed to confirm the effects that thyroid function had on kidney function. Second, the kidney function was estimated using a creatinine-based formula. Thyroid hormone status can affect the creatinine secretion of the kidney [52]. Therefore, studies using non-creatinine-based eGFR or measured GFR are needed to confirm our results. Third, TSH was measured once; therefore, laboratory error or a transient increase cannot be ruled out. Serum TSH values tend to return to normal more frequently in people with mild elevation (4–6 mIU/L) [53]. Forth, we speculated that the inverse relationship between fT4 and eGFR was due to reduced conversion of T4 into T3 via decreased deiodination. Although this speculation can be convinced with the T3 level, T3 level was not measured in KNHANES. Therefore, subsequent studies that check both T3 and T4 need to be followed to confirm our speculation. Finally, the homogenous ethnicity of the patients limits the generalizability of this study. Despite these limitations, our study has several strengths. This is the first study to demonstrate a nonlinear relationship between thyroid function and kidney function. Also, we are the first to suggest that the mediation effect of age on the relationship between fT4 and eGFR may be different from that of other conditions. Third, the large number of participants and the decent participation rate may strengthen the results of our study. In the future, we believe that well-designed prospective study about serial kidney function changes according to the thyroid hormone changes by replacement of thyroid hormone could provide a broader understanding of the relationship between thyroid hormone and kidney function.

In conclusion, increased TSH levels were associated with decreased eGFR, particularly in the reference range. The direct effect of increased fT4 levels, within the reference range, may be decreased eGFR; this suggests that functional hypothyroidism may be present at the tissue level, which was the case with TSH. Further studies need to be conducted to confirm the need for early replacement of thyroid hormones to protect kidney function.

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Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki, and full approval of the study was obtained from the IRB of the Korea Centers for Disease Control (IRB 2013-07CON-03-4C, 2013–12EXP-03-5C, 2015-01-02-6C). All KNHANES participants provided written informed consent to have their data used in research.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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