CLINICAL STUDY

Relationship between serum TSH levels and intrarenal hemodynamic parameters in euthyroid subjects

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Abstract

Objective: Low thyroid function may be associated with a reduced glomerular filtration rate (GFR) calculated on the basis of creatinine metabolism. Thyroid hormone directly affects serum creatinine in muscle and low thyroid function might exert a similar direct effect in the kidney. The goal of the study was to evaluate this possibility by assessment of the inulin-based GFR and to examine the mechanism underlying the reduction of GFR.

Patients and methods: Renal and glomerular hemodynamics were assessed by simultaneous measurements of plasma clearance of para-aminohippurate (C_{PAH}) and inulin (C_{in}) in 26 patients with serum creatinine <1.00 mg/dl and without thyroid disease. All subjects were normotensive with or without antihypertensive treatment and were kept in a sodium-replete state. Renal and glomerular hemodynamics were calculated using Gomez's formulae.

Results: Serum TSH, including within the normal range (0.69–4.30 μ IU/ml), was positively correlated with vascular resistance at the afferent arteriole (R_a) ($r=0.609$, $P=0.0010$), but not at the efferent arteriole (R_e). Serum TSH was significantly and negatively correlated with renal plasma flow (RPF), renal blood flow (RBF), and GFR ($r=-0.456$, $P=0.0192$; $r=-0.438$, $P=0.0252$; $r=-0.505$, $P=0.0086$ respectively). In multiple regression analysis, serum TSH was significantly positively associated with R_a after adjustment for age and mean blood pressure.

Conclusions: These findings suggest that low thyroid function, even within the normal range, is associated with reduced RPF, RBF, and GFR, which might be caused by a preferential increase in R_a .

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Introduction

Clinically overt and subclinical hypothyroidism is associated with a high rate of chronic kidney disease (CKD) (1, 2, 3, 4, 5, 6, 7) and is an established cardiovascular risk factor (1). Subclinical hypothyroidism occurs in 5–15% of the general population and is highly prevalent in women over 60 years of age (1, 2). We have found that patients with this condition have a significantly increased pulse wave velocity (PWV) (8), which suggests that subclinical hypothyroidism is a significant and independent cardiovascular risk factor (4), although the mechanism is uncertain. As these patients become older, the prevalence of CKD, a definite cardiovascular risk factor, increases along with an age-related increase in serum TSH levels (9).

A high serum TSH, even within its reference range, was recently found to be associated with a reduced glomerular filtration rate (GFR) calculated from formulae based on creatinine levels in serum and urine (6). Alteration in thyroid function affects muscle metabolism and may influence the creatinine-based

GFR, independently of its effect on the kidney, through an effect on metabolism of creatinine, which preferentially localizes in type II fibers in the muscle (10). Therefore, high serum TSH, even within the normal range, might directly suppress renal function and contribute to acceleration of atherosclerotic changes in subclinical hypothyroidism.

In this study, we examined the relationship of subtle changes in serum TSH within the normal range with inulin clearance (C_{in}), which is normally used for measurement of GFR. To examine the mechanism through which high serum TSH might reduce GFR, we simultaneously measured para-aminohippurate (PAH) clearance (C_{PAH}).

Patients and methods

Study design and patients

The study protocol was approved by the Ethics Committee of Osaka City University Graduate School of Medicine. The study was performed as a single-center

study at Osaka City University Hospital between January 2010 and August 2011. Written informed consent was obtained from each patient.

The subjects were 26 patients (55.4 ± 14.7 years old, 8 males and 18 females) who were admitted to Osaka City University Hospital for a medical checkup. Of these patients, 21 had diabetes, but none exhibited macroalbuminuria and all had a serum creatinine level <1.00 mg/dl. The mean serum TSH level was 1.720 ± 0.885 μ IU/ml and all patients were within the normal range of 0.69–4.30 μ IU/ml. Serum-free thyroxine (FT₄) and free triiodothyronine (FT₃) levels were also within the respective normal limits of 1.20 ± 0.182 ng/dl and 2.92 ± 0.38 pg/ml.

Measurement of C_{in} and C_{PAH} and calculation of intrarenal hemodynamic parameters

Renal plasma flow (RPF) and GFR were determined by the constant input clearance technique using PAH and inulin respectively. As shown in Fig. 1, continuous i.v. infusion of 1% inulin and 0.5% PAH from the antecubital vein was performed in the morning after an overnight fast, based on the method of Horio *et al.* (11). C_{in} and C_{PAH} were simultaneously measured using

Figure 1 Relationship between serum TSH, afferent arteriolar resistance (R_a) and efferent arteriolar resistance (R_e). Serum TSH had a significant positive correlation with R_a ($r=0.609$, $P=0.0010$) but showed no correlation with R_e ($r=0.013$, $P=0.9494$).

a simple method based on a single urine collection. In brief, patients received 500 ml water orally 15 min before infusion. After a priming dose of PAH and inulin, the rates of infusion were set at 300 ml/h for the first 30 min and 100 ml/min for the remaining time. To maintain hydration, 180 ml water was given. Patients completely emptied the bladder at 45 min after the start of the test and urine was collected for measurement of urinary inulin and PAH. The urine collection period was set at 90 min to increase the accuracy of the clearance study. Blood samples for measurement of serum inulin and PAH were taken at the beginning and end of the clearance period.

C_{in} and C_{PAH} were calculated by the UV/P method (U , concentration in urine; V , urine volume (ml/min); P , concentration in plasma) using the mean of the serum inulin concentrations at the beginning and end of the clearance period. Plasma PAH and inulin concentrations were determined colorimetrically using the N-1 naphthylethylenediamine and anthrone method respectively, with a Corning 258 spectrophotometer (4, 12, 13). The clearance values were not corrected for body surface area, partly because Turner & Reilly (14) have shown that adjusting renal hemodynamic variables for body surface may lead to inappropriate inferences and obscure gender-related differences.

Direct measurement of glomerular hemodynamics parameters in humans is not feasible, but formulae introduced by Gomez (15) (Table 1) allow indirect assessment of glomerular hemodynamics, as recently discussed in detail by Guidi *et al.* (16). These formulae were designed for quantitative estimation of filtration pressure across the glomerular capillaries (ΔP_F), glomerular hydrostatic pressure (P_{glo}), and afferent and efferent glomerular resistances (R_a and R_e respectively) using measured blood pressure, GFR measured by C_{in} , RPF measured by C_{PAH} , hematocrit, and plasma protein concentrations under the assumptions that: i) intrarenal vascular resistances can be divided into three compartments: afferent, efferent, and venular; ii) hydrostatic pressures in the venules, interstitium, renal tubules, and Bowman's space (P_{Bow}) are in equilibrium at a value of ~ 10 mmHg; iii) the gross filtration coefficient (K_{FG}) is 0.0406 ml/s per mmHg per kidney; and iv) a filtration disequilibrium is postulated along the glomerular capillaries (15, 16).

From Ohm's law:

$$R_a = ((MBP - P_{glo}) / RBF) \times 1328.$$

$$R_e = (GFR / K_{FG} (RBF - GFR)) \times 1328.$$

In these equations, 1328 is the conversion factor to dyne/s per cm^5 and GFR, RPF, and renal blood flow (RBF) are expressed in ml/s.

Statistical analysis

Results are expressed as means $\pm$ s.d. Correlations between two variables were examined using Spearman's correlation coefficient. Multiple regression analyses

Table 1 Gomez's formulae.

$$\begin{aligned}
FF &= GFR/RPF \\
RBF &= RPF/(1 - Ht) \\
R_a &= ((MBP - P_{glo})/RBF) \times 1328 \\
R_e &= (GFR/K_{FG} \times (RBF - GFR)) \times 1328 \\
P_{glo} &= \Delta P_F + P_{BOW} + \pi G \\
\Delta P_F &= GFR/K_{FG} \\
P_{BOW} &= 10 \text{ mmHg} \\
\pi G &= 5 \times (C_M - 2) \\
C_M &= TP/FF \times 1n(1/(1 - FF))
\end{aligned}$$

GFR, glomerular filtration rate (ml/min); RPF, renal plasma flow (ml/min); RBF, renal blood flow (ml/min); Ht, hematocrit; FF, filtration fraction; R_a , afferent (arteriolar) resistance (dyne/s per cm^5); R_e , efferent (arteriolar) resistance (dyne/s per cm^5); MBP, mean blood pressure calculated as $(2 \times \text{diastolic BP} + \text{systolic BP})/3$; K_{FG} , gross filtration coefficient (s/mmHg); P_{glo} , glomerular hydrostatic pressure (mmHg); ΔP_F , filtration pressure across the glomerular capillaries (mmHg); P_{BOW} , hydrostatic pressure in Bowman's space (10 mmHg); πG , oncotic pressure within glomerular capillaries (mmHg); C_M , plasma protein concentration within the glomerular capillaries (g/dl); TP, total protein concentration (g/dl).

were performed to evaluate the relationships between R_a and other parameters. All analyses were performed using StatView 5 for Windows (SAS Institute, Inc., Cary, NC, USA). The level of significance was set at $P < 0.05$.

Results

Baseline characteristics

Baseline characteristics of the 26 patients are shown in Table 2. The mean age was 59.5 ± 14.0 years old and eight patients (30.8%) were male. The mean levels of serum creatinine and blood urea nitrogen (BUN) were 0.692 ± 0.174 and 14.7 ± 2.8 mg/dl respectively and GFR estimated from C_{in} was 72.7 ± 18.3 ml/min. The mean blood pressure was normal (90.5 ± 10.7 mmHg), but 12 patients (46%) were receiving antihypertensive therapy with an angiotensin receptor blocker ($n=11$), angiotensin converting enzyme (ACE) inhibitor ($n=3$), or a calcium channel blocker ($n=5$). The plasma glucose and HbA1c values were 122.6 ± 34.2 mg/dl and $7.6 \pm 1.6\%$ respectively with 21 patients diagnosed with type 2 diabetes mellitus (DM) based on the history of diabetes or on criteria in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. There was no significant difference in GFR between patients with and without type 2 DM (DM vs non-DM: 70.9 ± 19.0 vs 80.1 ± 13.5 ml/min, $P=0.3203$). All subjects had no physical findings indicating thyroid disease, such as diffuse goiter, and the serum levels of FT_4 , FT_3 , and TSH were within the respective normal ranges of 1.200 ± 0.182 ng/ml, 2.924 ± 0.376 pg/ml, and 1.720 ± 0.885 μ IU/ml.

Relationship of serum FT_4 , FT_3 , and TSH with R_a , R_e , and glomerular hemodynamics

Serum TSH, even within its normal range, showed a significant positive correlation with R_a ($r=0.609$,

$P=0.0010$), but no correlation with R_e ($r=0.013$, $P=0.9494$) (Fig. 1), and had significant negative correlations with C_{in} -based GFR ($r=-0.505$, $P=0.0086$), RPF ($r=-0.456$, $P=0.0192$), and RBF ($r=-0.438$, $P=0.0252$) (Fig. 2). An age-related increase in serum TSH has been reported (17), but we found no significant correlation between age and R_a ($r=0.259$, $P=0.2015$) or R_e ($r=0.311$, $P=0.0647$). Collectively, these data suggest that a subtle change in serum TSH, even within its normal range might suppress glomerular hemodynamics, particularly by increasing vascular resistance at afferent arterioles, independent of age. Neither FT_4 nor FT_3 showed a significant relationship with R_a , R_e , C_{in} -based GFR, RPF, or RBF (data not shown).

Relationship of mean blood pressure with R_a , R_e , and glomerular hemodynamics

Mean blood pressure was significantly positively correlated with R_a ($r=0.422$, $P=0.0319$), but not with R_e ($r=0.043$, $P=0.8361$) (Fig. 3), suggesting that an increase in blood pressure might cause an increase in R_a , but not in R_e (15, 16). Mean blood pressure did not correlate significantly with RPF ($r=0.057$, $P=0.7812$) or RBF ($r=0.105$, $P=0.6098$), or with serum FT_4 ($r=0.207$, $P=0.3106$), FT_3 ($r=0.194$, $P=0.4004$), or TSH ($r=0.064$, $P=0.7648$). There was no significant difference in R_a between patients treated with a renin-angiotensin-aldosterone (RAS) system inhibitor and those who did not receive a RAS inhibitor (6406.8 ± 4540.9 vs 5572.2 ± 3592.6 , $P=0.6080$).

Table 2 Clinical characteristics of patients.

Item	Value (mean $\pm$ s.d.)	Range
Age	59.5 ± 14.0	22–78
Gender (m/f)	8/18	
Type 2 diabetes mellitus (yes/no)	21/5	
BMI (kg/m^2)	26.2 ± 4.5	18.3–35.0
Mean blood pressure (mmHg)	90.5 ± 10.7	71.3–119.3
Systolic blood pressure (mmHg)	127.1 ± 16.7	98–162
Diastolic blood pressure (mmHg)	72.2 ± 0.9	54–100
Serum creatinine (mg/dl)	0.692 ± 0.174	0.4–0.98
Blood urea nitrogen (mg/dl)	14.7 ± 2.8	9.0–21.0
Inulin clearance (ml/min)	72.7 ± 18.3	24.7–106.8
PAH clearance (ml/min)	362.6 ± 145.2	131–842
Albumin (g/dl)	4.1 ± 0.4	3.0–4.7
Plasma glucose (mg/dl)	122.6 ± 34.2	57.0–185.0
HbA1c (%)	7.6 ± 1.6	4.8–10.5
TSH (μ IU/ml)	1.720 ± 0.885	0.69–4.30
FT_3 (pg/ml)	2.924 ± 0.376	2.3–3.91
FT_4 (ng/dl)	1.200 ± 0.182	0.37–1.6

PAH, para-aminohippurate.

Figure 2 Relationship between serum TSH and glomerular filtration rate (GFR), renal plasma flow (RPF) and renal blood flow (RBF). Serum TSH showed significant negative correlations with (A) glomerular filtration rate (GFR; $r = -0.505$, $P = 0.0086$), (B) renal plasma flow (RPF; $r = -0.456$, $P = 0.0192$), and (C) renal blood flow (RBF; $r = -0.438$, $P = 0.0252$).

Multiple regression analysis of factors independently associated with R_a and R_e

The results of multiple regression analysis to identify factors significantly associated with R_a and R_e are shown in Table 3. In models including serum TSH, age, and mean blood pressure as independent variables, serum TSH alone emerged as a significant factor with a positive association with R_a but had no association with R_e .

Discussion

In this study, we clearly demonstrated that the high serum TSH, even within normal range, as reflected by a subtle increase in TSH within its normal range, was significantly correlated with reduction of GFR, RPF, and RBF, estimated from C_{in} and C_{PAH} . Our results may indicate a possible direct effect of TSH on the kidney, as it has been reported that TSH receptor is also expressed in a variety of extrathyroidal tissues including the kidney (18). Our results may be consistent with the report by Sun *et al.* (19), who demonstrated that TSH is an independent factor for determining renal function and CKD in normoglycemic euthyroid adults. The underlying mechanism of our results may involve increased vascular resistance at afferent arterioles, based on the significant and independent association of high serum TSH with increased R_a , independent of age and mean blood pressure, but not with R_e . The parameters for renal hemodynamics were calculated from C_{in} and C_{PAH} , which are independent of creatinine metabolism. Therefore, this shows that the effect of low thyroid function on creatinine metabolism in muscle and the resultant changes of serum and urinary creatinine levels are not responsible for low GFR in patients with low normal thyroid function. Causality is not conclusively determined, but it is likely that low thyroid function may reduce GFR, RPF, and RBF by increasing R_a , as it has been shown that T_4 replacement therapy increases GFR in hypothyroid patients (20) and that treatment of Graves' patients with anti-thyroid drugs decreases GFR (21). Our study may also be consistent with the results that TSH positively correlated with creatinine in hypothyroid subjects (22). Low cardiac output may also be associated with decreased RBF in hypothyroidism (23).

We have previously reported a significant increase in arterial wall stiffening, as represented by an increase in PWV, in patients with subclinical hypothyroidism (24) and clinically overt hypothyroidism (25). As the current study raised the possibility that CKD might develop due to low thyroid function, it is possible that development of CKD in patients with low thyroid function (but within the normal range) might be an early event that accelerates atherosclerotic changes, which develop no earlier than subclinical hypothyroidism (26). Therefore,

Figure 3 Relationship between mean blood pressure and afferent arteriolar resistance and efferent arteriolar resistance. Mean blood pressure had a significant positive correlation with afferent arteriolar resistance (R_a ; $r=0.422$, $P=0.0319$) but showed no correlation with efferent arteriolar resistance (R_e ; $r=0.043$, $P=0.8361$).

CKD due to low thyroid function may contribute to development of atherosclerotic changes in subclinical hypothyroidism.

In humans, it is not possible to measure glomerular hemodynamic variables directly; thus, the evidence for this pathogenetic mechanism is indirect and is based mainly on therapeutic interventions that are believed to lower glomerular pressure and filtration, such as a low-protein diet or ACE inhibitors (27). However, in 1951, Gomez (15) published a series of formulae for indirect evaluation of glomerular hemodynamics in humans. These formulae (slightly modified for animal studies) have been used to calculate glomerular hemodynamics in various conditions, including untreated and treated essential hypertension (15, 28), rat models of hypertension (28), renovascular hypertension (29), primary aldosteronism (30), and supraventricular tachycardia (31). In this study, on the basis of these formulae, we found that reduced GFR, RPE, and RBF mainly result from increased vascular resistance at afferent arterioles, as reflected by increased R_a .

Table 3 Multiple regression analysis of factors with a potential independent association with afferent arteriolar resistance (R_a) and efferent arteriolar resistance (R_e).

	R_a		R_e	
	β	P	β	P
Serum TSH	0.528	0.0042	−0.103	0.6395
Age	0.064	0.6977	0.294	0.1846
Mean blood pressure	0.304	0.706	−0.024	0.9111
R^2	0.330		0.0777	

This study has some limitations. First, the study was performed in a small number of Japanese patients, and a large-scale study is needed to confirm that the subtle reduction of thyroid function within euthyroidism increases R_a and decreases C_{in} . Secondly, some of the patients took antihypertensive drugs, including RAS inhibitors. However, these inhibitors mainly affect efferent arterioles and decrease R_e (32, 33), and their use cannot explain the increase in R_a . Thirdly, diabetic patients were included in the study. However, in our recent study, glycemic control indices were significantly positively associated with R_e , but not with R_a (data not shown). Also, patients with DM did not show micro-albuminuria and there was no significant difference in GFR between diabetic and non-diabetic patients, which indicates that diabetic nephropathy did not influence the results. Lastly, the formulae used to evaluate glomerular hemodynamics in humans are based on several assumptions, but many studies have validated the clinical utility of these formulae, as described earlier.

In conclusion, the results of the study demonstrate that low thyroid function, even within the normal range, is associated with reduced GFR, RPE, and RBF, resulting from increased R_a , and thus suggest that development of CKD might promote atherosclerotic changes in the early stage of hypothyroidism.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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