Association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus

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Abstract. Subclinical hypothyroidism (SCH) has been associated with type 2 diabetes mellitus. However, it is unknown whether common complications of type 2 diabetes, such as diabetic nephropathy, are also present with SCH. Here, we investigated the association between SCH and diabetic nephropathy among Japanese patients with type 2 diabetes mellitus. In this multicenter cross-sectional study, we recruited 414 such patients who had no previous history of thyroid disease. Serum thyroid hormone levels and the urinary albumin:creatinine ratio were measured. SCH was defined as an elevated thyroid-stimulating hormone (TSH) level (>4.0 mIU/L), and diabetic nephropathy was defined as urinary albumin/creatinine ratio ≥300 mg/g. The prevalence of SCH was 8.7% (n = 36) among patients with type 2 diabetes mellitus. The SCH group had a higher prevalence of dyslipidemia (p = 0.008) and diabetic nephropathy (p = 0.014) than the euthyroid group. Multivariate analysis identified significant positive associations between diabetic nephropathy and SCH (odds ratio [OR], 3.51; 95% confidence interval [CI], 1.10–10.0; p = 0.034), hypertension (OR, 4.56; 95% CI, 1.69–14.7; p = 0.001), and smoking (OR, 3.02; 95% CI, 1.14–7.91; p = 0.026). SCH may be independently associated with diabetic nephropathy in Japanese patients with type 2 diabetes mellitus.

Key words: Dyslipidemia, Kidney, Metabolic disease, Microvascular disease, Thyroid-stimulating hormone

THE MEDICAL costs associated with hemodialysis in Japan represent an economic concern. Given that diabetic nephropathy is the primary indication for hemodialysis in Japan, prevention of disease progression is necessary to reduce the number of patients on dialysis.

Subclinical hypothyroidism (SCH) occurs when serum TSH levels are elevated but free T4 (FT4) concentrations remain within the normal range. Although SCH is usually asymptomatic, it has been associated with hyperlipidemia [1], atherosclerosis [2, 3], cardiac dysfunction [4], and overt hypothyroidism [5]. An association between type 2 diabetes mellitus and SCH is not uncommon, with an SCH prevalence of 2.2–17% reported in previous studies [6-8]. Previous studies have also shown a close interrelationship between chronic kidney disease (CKD) and SCH [9, 10]. Furthermore, the efficacy of thyroid hormone replacement in CKD patients with SCH has been reported [11].

There are only a few reports regarding an association between SCH and diabetic nephropathy [12-14].
In 159 Japanese patients with type 2 diabetes mellitus recruited from an inpatient clinic, high levels of TSH were associated with the development of albuminuria [13]; therefore, SCH may contribute to the development of diabetic nephropathy among Japanese patients with type 2 diabetes mellitus. However, the results are inconsistent; thus, the association between SCH and diabetic nephropathy remains unclear.

In this study, we aimed to determine the relationship between SCH and diabetic nephropathy in Japanese patients with type 2 diabetes mellitus.

Materials and Methods

Study population
The Dogo Study was a multicenter prospective cohort study that recruited 513 Japanese patients with previously diagnosed type 2 diabetes mellitus (median age at recruitment, 62.0 years; range, 20–85 years; 56.9% men) whose thyroid function was assessed between September 2009 and December 2010. The Dogo Study Group consisted of medical doctors who specialize in diabetes mellitus at 10 hospitals in Ehime prefecture, Shikoku Island, Japan. Type 2 diabetes mellitus was diagnosed according to the Japan Diabetes Society criteria. SCH was defined as an elevated TSH level (>4.0 mIU/L) and a normal FT4 level (0.90–1.70 ng/dL). Exclusion criteria included a history of thyroid disease with or without treatment, cardiac disease, acute infection, stage 4 and 5 CKD, and liver disease. After excluding 99 patients, a total of 414 patients were included in the study. The present study protocol received ethical approval from the institutional review board of Ehime University. Written informed consent was obtained from all patients enrolled in the study.

Clinical examination and laboratory measurements
All participants completed self-administered questionnaires about diabetes duration, daily alcohol intake, daily number of cigarettes smoked, use of antihypertensive medication, and use of anti-hyperlipidemic medication. Body mass index (BMI) was calculated as weight (kg) divided by the square of height in meters (m²). Patients who smoked ≥1 cigarette per day were regarded as current smokers. Blood pressure was measured with a cuff in the sitting position after a rest period of more than 5 min. Hypertension was defined by a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mmHg, or both, or if the patient was already taking anti-hypertensive drugs. Dyslipidemia was defined by a serum total cholesterol concentration >220 mg/dL, triglyceride concentration >140 mg/dL, or high-density lipoprotein (HDL) cholesterol concentration <40 mg/dL, or if the patients were already being treated with lipid-lowering agents. Stroke and ischemic heart disease were assessed using the results of self-administered questionnaires, medical records, and admission data. The levels of TSH and T4 were measured using COBAS® (Roche, West Sussex, UK).

Assessment of estimated glomerular filtration rate and the definition of chronic kidney disease
Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine (mg/dL): 194 × serum Cr⁻¹.⁰⁹⁴ × age⁻⁰.⁴⁸⁷ × 0.⁷³⁹ (if female) [15]. CKD was defined as eGFR <60 mL/min/1.73 m².

Assessment of nephropathy associated with type 2 diabetes mellitus
Nephropathy was defined using the urinary albumin:creatinine ratio (UACR) to classify the participants as follows: normoalbuminuria, 0-29.9 mg/g creatinine; microalbuminuria, 30-299 mg/g creatinine; and nephropathy, ≥300 mg/g creatinine [16]. The UACR was calculated using the first urine sample taken on the morning.

Statistical analysis
All numerical variables are expressed as mean ± standard deviation. Statistical analyses were conducted using unpaired student’s t-tests, Chi-square tests, or one-way analysis of variance. One-way analysis of variance, followed by the Tukey’s multiple comparison test, was used for comparisons between groups. We used multivariate logistic regression models to estimate the odds ratio (OR) for the presence of diabetic nephropathy. All statistical analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA). All probability values for statistical tests were two-tailed, and p < 0.05 was considered statistically significant.

Results
The prevalence of SCH was 8.7% (36/414) among patients with type 2 diabetes mellitus (Table 1). The SCH group had a higher prevalence of dyslipidemia (p = 0.008) and diabetic nephropathy (p = 0.014) than the euthyroid group. eGFR in the SCH group was lower
Subclinical hypothyroidism in diabetes

Subclinical hypothyroidism in diabetes was associated with higher creatinine levels than the normal and microalbuminuria groups ($p < 0.05$ for both) and longer duration of type 2 diabetes mellitus than the normal group ($p < 0.05$). eGFR in the diabetic nephropathy and microalbuminuria groups was lower than that in the normal group. In the diabetic nephropathy group, the ratio of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use was higher than that in the normal and microalbuminuria groups ($p = 0.001$).

The prevalence of diabetic nephropathy was 7.0% (29/414) in this cohort (Table 2). Mean age in the microalbuminuria group was higher than that in the normal group ($p < 0.05$). Diabetic nephropathy patients had higher glycated hemoglobin (HbA1c) and creatinine levels than the normal and microalbuminuria groups ($p < 0.05$ for both) and longer duration of type 2 diabetes mellitus than the normal group ($p < 0.05$). eGFR in the diabetic nephropathy and microalbuminuria groups was lower than that in the normal group. In the diabetic nephropathy group, the ratio of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use was higher than that in the normal and microalbuminuria groups ($p = 0.001$).

**Table 1** Clinical characteristics of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 414)</th>
<th>Euthyroid (n = 378)</th>
<th>SCH (n = 36)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.3 ± 11.3</td>
<td>61.1 ± 11.3</td>
<td>63.7 ± 11.1</td>
<td>0.331</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>61.4</td>
<td>60.8</td>
<td>66.7</td>
<td>0.859</td>
</tr>
<tr>
<td>BMI</td>
<td>25.2 ± 4.8</td>
<td>25.1 ± 4.8</td>
<td>26.1 ± 4.4</td>
<td>0.094</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.22 ± 1.46</td>
<td>7.17 ± 1.42</td>
<td>7.76 ± 1.75</td>
<td>0.061</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.82 ± 0.22</td>
<td>0.79 ± 0.22</td>
<td>0.86 ± 0.26</td>
<td>0.140</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m$^2$)</td>
<td>74.7 ± 20.6</td>
<td>75.3 ± 20.5</td>
<td>68.3 ± 20.5</td>
<td>0.031</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>20.8</td>
<td>21.7</td>
<td>11.1</td>
<td>0.135</td>
</tr>
<tr>
<td>Drinking (%)</td>
<td>41.4</td>
<td>41.5</td>
<td>41.6</td>
<td>0.987</td>
</tr>
<tr>
<td>Duration of T2DM (years)</td>
<td>11.3 ± 9.6</td>
<td>11.4 ± 9.6</td>
<td>10.3 ± 9.2</td>
<td>0.462</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>48.1</td>
<td>48.0</td>
<td>55.6</td>
<td>0.359</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>42.5</td>
<td>40.5</td>
<td>63.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Cerebral infarction (%)</td>
<td>6.0</td>
<td>5.8</td>
<td>8.3</td>
<td>0.601</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>8.9</td>
<td>9.3</td>
<td>5.6</td>
<td>0.452</td>
</tr>
<tr>
<td>Diabetic nephropathy (%)</td>
<td>7.0</td>
<td>6.1</td>
<td>16.7</td>
<td>0.014</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>32.8</td>
<td>32.0</td>
<td>41.9</td>
<td>0.198</td>
</tr>
<tr>
<td>Thyroid auto-antibody (%)</td>
<td>5.1</td>
<td>4.5</td>
<td>11.1</td>
<td>0.111</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>39.9</td>
<td>38.9</td>
<td>50.0</td>
<td>0.204</td>
</tr>
</tbody>
</table>

BMI, body mass index; SCH, subclinical hypothyroidism; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

**Table 2** Clinical characteristics of the study participants according to renal function

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 278)</th>
<th>Microalbuminuria (n = 107)</th>
<th>Diabetic nephropathy (n = 29)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6 ± 10.7</td>
<td>64.4 ± 11.3*</td>
<td>61.1 ± 11.5</td>
<td>0.014</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>60.1</td>
<td>61.6</td>
<td>72.4</td>
<td>0.458</td>
</tr>
<tr>
<td>BMI</td>
<td>24.8 ± 4.7</td>
<td>25.7 ± 4.5</td>
<td>25.8 ± 6.2</td>
<td>0.207</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.14 ± 1.48</td>
<td>7.17 ± 1.31</td>
<td>8.21 ± 1.57**</td>
<td>0.006</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.75 ± 0.20</td>
<td>0.84 ± 0.24</td>
<td>1.04 ± 0.38***</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m$^2$)</td>
<td>77.8 ± 19.4</td>
<td>69.8 ± 19.5*</td>
<td>62.5 ± 28.3*</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>18.7</td>
<td>22.4</td>
<td>34.5</td>
<td>0.042</td>
</tr>
<tr>
<td>Drinking (%)</td>
<td>40.7</td>
<td>42.9</td>
<td>44.8</td>
<td>0.421</td>
</tr>
<tr>
<td>Duration of T2DM (years)</td>
<td>11.1 ± 9.2</td>
<td>12.7 ± 10.9</td>
<td>14.2 ± 8.9*</td>
<td>0.023</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>38.9</td>
<td>65.4</td>
<td>72.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>40.3</td>
<td>43.9</td>
<td>58.9</td>
<td>0.031</td>
</tr>
<tr>
<td>Cerebral infarction (%)</td>
<td>5.4</td>
<td>7.5</td>
<td>6.9</td>
<td>0.431</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>8.3</td>
<td>10.3</td>
<td>10.3</td>
<td>0.758</td>
</tr>
<tr>
<td>Thyroid auto-antibody (%)</td>
<td>4.3</td>
<td>4.7</td>
<td>6.8</td>
<td>0.421</td>
</tr>
<tr>
<td>SCH (%)</td>
<td>7.6</td>
<td>8.4</td>
<td>20.7</td>
<td>0.047</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>32.0</td>
<td>49.5</td>
<td>79.3**</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index; SCH, subclinical hypothyroidism; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

Differences were analysed by ANOVA, followed by Tukey’s test * $p < 0.05$ versus normal; ** $p < 0.05$ versus microalbuminuria.
Next, we investigated a possible relationship between SCH and renal function (Table 3). In the sex- and age-adjusted models (model 1), SCH was positively associated with diabetic nephropathy (OR, 3.34; 95% confidence interval [CI], 1.15–8.54; \( p = 0.030 \)). After adjustment for sex, age, duration of type 2 diabetes mellitus, hypertension, and SCH (model 2), SCH was positively associated with diabetic nephropathy (OR, 3.44; 95% CI, 1.14–9.35; \( p = 0.030 \)), as was hypertension (OR, 4.56; 95% CI, 1.69–14.7; \( p = 0.001 \)). After adjustment for sex, age, BMI, hypertension, dyslipidemia, current smoking, current drinking, and duration of type 2 diabetes mellitus (model 3), multivariate analysis identified a positive association between SCH and diabetic nephropathy (OR, 3.51; 95% CI, 1.10–10.0; \( p = 0.034 \)), hypertension (OR, 4.56; 95% CI, 1.69–14.7; \( p = 0.001 \)), and smoking (OR, 3.02; 95% CI, 1.14–7.91; \( p = 0.026 \)).

Furthermore, we analyzed the association between SCH and CKD (Table 3). In model 1, age was independently associated with CKD (OR, 1.06; 95% CI, 1.04–1.10; \( p = 0.001 \)), while SCH was not associated with CKD (OR, 1.68; 95% CI, 0.75–3.59; \( p = 0.190 \)). In model 2, both age (OR, 1.04; 95% CI, 1.03–1.08; \( p = 0.001 \)) and hypertension (OR, 2.20; 95% CI, 1.33–3.68; \( p = 0.002 \)) were independently associated with CKD, while SCH was not associated with CKD (OR, 1.75; 95% CI, 0.77–3.83; \( p = 0.164 \)). In model 3, age (OR, 1.05; 95% CI, 1.02–1.07; \( p = 0.001 \)), hypertension (OR, 1.83; 95% CI, 1.07–3.17; \( p = 0.027 \)), and dyslipidemia (OR, 2.58; 95% CI, 1.53–4.38; \( p = 0.001 \)) were independently associated with CKD. SCH was not associated with CKD (OR, 1.34; 95% CI, 0.58–3.02; \( p = 0.478 \)).

Our results show that SCH was associated with the presence of diabetic nephropathy among 414 patients with type 2 diabetes mellitus. The prevalence of SCH was 8.7% among patients with type 2 diabetes mellitus (n = 414), and the prevalence of SCH among patients with diabetic nephropathy was 20.7% (n = 29). Moreover, the multivariate analysis resulted in an independent association between SCH and diabetic nephropathy. In the SCH group, eGFR was lower than that in the euthyroid group. However, SCH was not independently associated with CKD in the multivariate analysis.

With regards to other microvascular complications, the results of previous studies that assessed the associa-
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orders, which could have affected their results.

In the same study conducted in Korea, the duration of diabetes (6.9 ± 6.6 years, euthyroid group; 8.9 ± 7.2 years, SCH group) was shorter than that in the present and other previous studies. Moreover, the mean age (66.3 ± 10.7 years, euthyroid group; 67.2 ± 10.8 years, SCH group) of the patients in a previous study conducted in China was older than other previous studies. Age and duration of diabetes were risk factor for diabetic nephropathy.

Furthermore, differences between studies might be explained by the differing definitions of diabetic nephropathy. In the present study and the Korean study, diabetic nephropathy was defined according to the American Diabetes Association criteria, with reported diabetic nephropathy prevalence of 7.0% and 6.4% [12], respectively. However, in the Chinese study, nephropathy was defined using creatinine and albuminuria grade [14], and the prevalence of diabetic nephropathy was considerably higher (48.6%).

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Clinical characteristics among previous studies that examined the association SCH and diabetic nephropathy</th>
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</thead>
<tbody>
<tr>
<td>Country</td>
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<tr>
<td>Number</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Age (Euthyroid, years)</td>
<td></td>
</tr>
<tr>
<td>Age (SCH, years)</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td></td>
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<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>BMI (Euthyroid)</td>
<td></td>
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<tr>
<td>BMI (SCH)</td>
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<tr>
<td>Duration of DM (years)</td>
<td></td>
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<tr>
<td>Duration of DM (Euthyroid, years)</td>
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<tr>
<td>Duration of DM (SCH, years)</td>
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<tr>
<td>HbA1c (%)</td>
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<tr>
<td>HbA1c (Euthyroid, %)</td>
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<tr>
<td>HbA1c (SCH, %)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
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<tr>
<td>Creatinine (Euthyroid, mg/dL)</td>
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<tr>
<td>Creatinine (SCH, mg/dL)</td>
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<tr>
<td>eGFR (mL/min/1.73m²)</td>
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</tr>
<tr>
<td>eGFR (Euthyroid, mL/min/1.73m²)</td>
<td></td>
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<tr>
<td>eGFR (SCH, mL/min/1.73m²)</td>
<td></td>
</tr>
<tr>
<td>SCH (%)</td>
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<tr>
<td>Diabetic nephropathy (%)</td>
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<tr>
<td>Diabetic nephropathy (Euthyroid, %)</td>
<td></td>
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<tr>
<td>Diabetic nephropathy (SCH, %)</td>
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<tr>
<td>The definition of diabetic nephropathy</td>
<td></td>
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<tr>
<td>The definition of SCH</td>
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</tbody>
</table>

Data are presented as n (%) or mean (SD). BMI, body mass index; DM, diabetes mellitus; SCH, subclinical hypothyroidism; eGFR, estimated glomerular filtration rate; ADA, American diabetes association; Cr, creatinine
Furthermore, diabetic nephropathy was not evaluated in all of the cases in the Korean and Chinese studies or in other previous studies. For example, Yasuda et al. reported an association between serum TSH levels and logarithmically transformed UACR values and demonstrated that serum TSH levels were independently associated with albuminuria among Japanese patients with diabetes mellitus [13]. However, diabetic nephropathy was not diagnosed, and the sample size was smaller than other studies and consisted of only inpatients [13].

Finally, the baseline HbA1c levels in other studies were higher than in our cohort, and higher HbA1c levels have been shown to be a significant predictor of albuminuria among patients with newly diagnosed type 2 diabetes mellitus [19].

Previous studies have demonstrated a strong association between eGFR and TSH, including a negative correlation between eGFR and TSH concentration [20-22], a close interrelationship between CKD and SCH [9, 10, 14, 20], a high prevalence of CKD among patients with SCH [20] in the general population, and the efficacy of thyroid replacement therapy in attenuating the rate of eGFR decline among patients with CKD that also included patients with diabetes mellitus (38.9%) [21]. However, to the best of our knowledge, no study has investigated the association between SCH and eGFR among patients with type 2 diabetes mellitus. Although SCH was not an independent factor for CKD, after adjustment for several factors, eGFR in the SCH group was lower than that in the euthyroid group in the present study.

In general, smoking and hypertension are well known risk factors for renal dysfunction among patients with type 2 diabetes mellitus [23, 24]. In the multivariate analysis in the present study, smoking and hypertension were independently associated with diabetic nephropathy. Dyslipidemia also plays an important role in the progression of kidney dysfunction and has been shown to be an independent risk factor for end stage renal disease in the RENAAL Study [25]. Additionally, in patients with SCH, lipid metabolism is commonly observed [26, 27]. In the present study, the prevalence of dyslipidemia in the SCH group was higher than that in the euthyroid group, and the multivariate analysis resulted in a marginally significant association between dyslipidemia and diabetic nephropathy ($p = 0.088$).

Our study has some limitations. First, this was a cross-sectional study; thus, we failed to establish a causal relationship between SCH and diabetic nephropathy. Thyroid hormones affect nearly all of the organ systems in the body, including the renal system [28]; conversely, renal function affects the thyroid gland [29]. However, thyroid hormone replacement therapy could attenuate the decline in renal function in CKD patients with SCH, including those with diabetic nephropathy [21]. Second, most of the participants had received diabetes treatment for several years, and half of this cohort had received anti-hypertensive agents. Hypertension is a known risk factor for diabetic nephropathy and was also associated with diabetic nephropathy in the present study. Third, the number of patients with SCH and diabetic nephropathy was not sufficient for detailed analysis. Finally, thyroid function and UACR were measured at a single time point.

In conclusion, SCH may be independently associated with diabetic nephropathy in Japanese patients with type 2 diabetes mellitus. These findings imply that SCH may be a new therapeutic target to prevent the development and progression of renal disease in diabetes patients. Thyroid function screening should be offered to diabetes patients with diabetic nephropathy. Further longitudinal research is necessary to determine the causal relationship between SCH and diabetic nephropathy.

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Disclosure
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Author Contributions
SY, YT, KM, TM, TU, TN, TS, MT, TK, SM, TS, HM, HM, BM, YH, MO, and TT conducted the research; TK and TT reviewed and edited the manuscript; and TK and TT reviewed the manuscript.

References
ing of renal function in hypothyroid patients?


