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Effects of Subclinical Hypothyroidism on Nephropathy Complicating Type 2 Diabetes: The Fremantle Diabetes Study Phase II

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Abstract

Context: It is uncertain whether subclinical hypothyroidism (SCH) contributes to intrinsic renal dysfunction in people with type 2 diabetes mellitus (T2DM).

Objective: To investigate whether SCH persisting over 4 years is associated with incident impairment of renal function in people with T2DM.

Design: Longitudinal observational study.

Setting: Urban population of people with type 2 diabetes living in the community and enrolled in a prospective observational study of diabetes.

Participants: 725 without known thyroid dysfunction at baseline and at follow-up.

Main Outcome Measures: Changes in estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (ACR) in participants stratified by thyroid status at baseline and follow-up into those with euthyroidism or transient or persistent subclinical (SCH)/overt hypothyroidism.

Results: After a mean ± SD 4.3 ± 0.4 years, 683 participants had stable euthyroidism, 18 transient SCH/overt hypothyroidism, and 24 persistent SCH/overt hypothyroidism. No significant changes in eGFR were observed in any group. Those with persistent SCH/overt hypothyroidism demonstrated a significant increase in ACR, which was not seen in those with euthyroidism and transient SCH/overt hypothyroidism (ΔACR 22.0 ± 81.4 vs 0.4 ± 36.7 and −0.3 ± 5.7 mg/mmol, respectively, $P = .027$). Similar results were seen when those with baseline ACR > 30 mg/mmol were excluded.

Conclusion: Persistent SCH/overt hypothyroidism was associated with incident increased albuminuria not observed in euthyroid participants. Assessment of thyroid function in all patients with T2DM may be indicated, as some previous studies provide evidence that thyroxine replacement may ameliorate albuminuria.

Key Words: type 2 diabetes, subclinical hypothyroidism, renal function, albuminuria, temporal trends, community-based, longitudinal study

The relationship between subclinical hypothyroidism (SCH) and renal dysfunction is unclear. A reduced estimated glomerular filtration rate (eGFR) has been associated with SCH in cross-sectional studies in both the general population (1, 2) and people with type 2 diabetes (3). However, longitudinal general population studies do not show a clear relationship between baseline depressed thyroid function and a subsequent accelerated decline in renal function (1, 4). Interpretation of these data is complicated by the fact that SCH is frequently transient (5, 6). It is, therefore, possible that its potential effects on eGFR are reversible once hypothyroidism-associated reduced cardiac output and renal plasma flow resolve (7). A prospective study of proteinuric patients with chronic kidney disease (CKD) and SCH found that thyroid replacement therapy stabilized the decline in eGFR (8) while, in another study in patients with CKD, renal dysfunction deteriorated at a faster rate in those with persistent SCH than in individuals whose SCH resolved or who remained euthyroid (9). Nevertheless, in a study of children with type 1 diabetes, a prolonged period of hypothyroidism was associated with a reduced eGFR that was not fully corrected with thyroxine replacement therapy (10).

Increased urinary albumin excretion is a manifestation of CKD complicating diabetes, but it can also reflect coincident insulin resistance, hypertension, and cardiovascular disease (11). There is evidence of a cross-sectional association between SCH and albuminuria in some studies of type 2 diabetes (12-14) but not others (15), while thyroid replacement therapy in patients with CKD and SCH or overt hypothyroidism was associated with a reduction in proteinuria (8, 16). Given that SCH can be associated with insulin resistance (17) and hypertension (18), the benefits of treatment of SCH for albuminuria may be through these risk factors rather than through a direct effect on CKD pathophysiology in type 2 diabetes.

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Whether SCH contributes independently to progressive renal dysfunction and/or albuminuria is an important question, as the role of thyroid replacement therapy for SCH remains controversial (19) and guidelines recommend against thyroid function testing solely because a patient has type 2 diabetes (20). If SCH has significant clinical implications, there may be an argument for enhanced screening and more intensive management. In light of these considerations, the aim of the present study was to test the hypothesis that persistent SCH is associated with faster decline in eGFR and a more rapid increase in urinary albumin excretion than transient SCH in patients with type 2 diabetes.

Materials and Methods

Participants and Approvals

The Fremantle Diabetes Study Phase II (FDS2) is a prospective observational cohort study of representative community-based people living with diabetes in the primary catchment area of Fremantle Hospital in the state of Western Australia (21). The FDS2 cohort comprises 1668 participants with diabetes residing in the study area (population ≈150 000) at the time of recruitment between 2008 and 2011, including 1431 (85.8%) with type 2 diabetes based on detailed clinical, laboratory, and genetic features (22). For the purposes of the present study, we included FDS2 participants with type 2 diabetes who (1) had no known thyroid disease at baseline (15); (2) were not treated with lithium or amiodarone at study entry; (3) had no missing baseline sera or medication data; and (4) had valid serum creatinine, free T4 (FT4) and TSH, and urine albumin and creatinine concentrations at baseline and 4 years after study entry. In addition, FDS2 participants who were euthyroid at entry and hypothyroid at follow-up were excluded. The FDS2 protocol was approved by the Southern Metropolitan Area Health Service Human Research Ethics Committee. All subjects gave informed consent before participation.

Baseline and Follow-up Assessments

Assessments at entry and at each biennial in-person review included a comprehensive questionnaire, a detailed physical examination by trained registered nurses, and fasting biochemical tests performed in a single nationally accredited laboratory (21). In addition to details of all medical conditions, demographic, socioeconomic, and lifestyle data were recorded. Full details of all medications were recorded. Racial/ethnic background was categorized based on self-selection; country/countries of birth and parents'/grandparents' birth; and language(s) spoken at home as Anglo-Celt, Southern European, Other European, Asian, Aboriginal, or mixed/other. Smoking, alcohol consumption and vaccination histories were documented. Body mass index was determined together with A Body Shape Index, which represents a more reliable estimate of visceral adiposity (23). Complications were identified using standard definitions (24). Baseline complications status was used to calculate the Charlson Comorbidity Index (24) excluding diabetes-specific chronic complications (25).

Laboratory Assays

Standard of care testing of serum glucose, hemoglobin A1c (HbA_{1c}), serum urea electrolytes and creatinine, serum lipids, serum uric acid, liver function, urine albumin, and creatinine were performed using standard automated methods. Albuminuria was assessed by early-morning spot urine albumin:creatinine ratio (ACR) measurement, and renal function was assessed from the estimated glomerular filtration rate (eGFR) (26). eGFR was calculated using the CKD-EPI algorithm (26). Spot urine albumin excretion was expressed as ACR in mg/mmol.

Serum TSH and FT4 were assessed in samples collected at baseline and at the second biennial (year 4) review visit. Antibodies to thyroperoxidase (anti-TPO) were measured at baseline only. TSH, FT4, and anti-TPO were measured by automated electrochemiluminescence immunoassays using reagents from Roche Diagnostics Australia (Castle Hill, NSW, Australia) and a Cobas E601 analyzer. Between-run imprecision, expressed as coefficients of variation, were ≤4.7% for FT4, ≤3.5% for TSH, and ≤8.1% for anti-TPO antibodies. Reference intervals were 0.34 to 5.1 mIU/L for serum TSH, 12 to 22 pmol/L for serum FT4, and <35 U/L for anti-TPO. SCH and overt hypothyroidism were defined as a TSH >5.1 mU/L, with FT4 ≥12 pmol/L and <12 pmol/L, respectively. Participants were classified as stable euthyroid, transient, or persistent hypothyroidism in the absence of incident thyroid replacement therapy. Transient hypothyroidism was defined as SCH or overt hypothyroidism at baseline with normal TSH and FT4 at year 4, whereas persistent hypothyroidism was defined as baseline SCH or overt hypothyroidism with SCH or overt hypothyroidism at year 4.

Serum N-terminal pro-brain natriuretic peptide was measured on an Elecsys 2010 (Roche Diagnostics Australia). Serum C-reactive protein was measured on an Architect ci16200 analyzer (Abbott Diagnostics Australia, North Ryde, NSW, Australia) using a high-sensitivity protocol with reagents supplied by Abbott Diagnostics.

Measures of Insulin Resistance

Insulin resistance was calculated by 2 methods. The estimated glucose disposal rate (eGDR) was calculated as $21.158 - (0.09 \times WC) - (3.407 \times HT) - (0.551 \times HbA_{1c})$ where WC is waist circumference (cm) and HT is hypertension (yes = 1/no = 0; treatment with antihypertensive medication or systolic blood-pressure > 140 mmHg or diastolic blood-pressure > 90 mmHg, respectively), and HbA_{1c} is percentage by the Diabetes Control and Complications Trial (27) as validated for use in type 2 diabetes (28). The Homoeostasis Model Assessment Index of Insulin Resistance was calculated from fasting plasma glucose and insulin concentrations as described previously (29).

Statistical Analysis

Data are summarized as proportions, mean ± SD, geometric mean (SD range), or median [interquartile range] as appropriate. For independent samples, 2-way comparisons for proportions were by Fisher's exact test, for normally distributed variables by Student's *t*-test, and for nonnormally distributed variables by Mann-Whitney *U*-test. Three-way comparisons for proportions were by the Fisher-Freeman-Halton exact or chi-squared tests, for normally distributed variables by ANOVA, and for nonnormally distributed variables by the Kruskal-Wallis test. Where the overall trend for these multiple comparisons was statistically significant, post hoc Bonferroni-corrected pairwise comparisons were performed.

Multinomial regression was used to identify independent associates of hypothyroidism status defined at baseline and

year 4 with the euthyroid group as reference. Binomial logistic regression analysis was undertaken to further investigate differences in the characteristics of transient and persistent hypothyroidism groups. Clinically relevant and biologically plausible variables were considered for model entry if bivariable $P < .20$. All statistical analyses were performed using SPSS for Windows (version 29; SPSS Inc., Chicago, IL, USA).

Results

Baseline Participant Characteristics

The characteristics of the 725 participants in the present study stratified by their thyroid status at baseline and at follow-up after 4.3 ± 0.4 years are shown in Table 1. Of the 18 with transient SCH or overt hypothyroidism, 3 (16.7%) had transient overt hypothyroidism, and of the 24 with persistent SCH or overt hypothyroidism, 3 (12.5%) had overt hypothyroidism at baseline and year 4. None of these 6 participants had a TSH > 8.2 mU/L or FT4 < 10.4 pmol/L, and none were started on thyroxine replacement during follow-up; these very small numbers with mild disease justify their combination with the SCH cases in both groups.

The participants with persistent SCH or overt hypothyroidism were relatively lean and less likely to be treated with antihypertensive agents than the other groups. They had relatively low gamma glutamyltransferase levels but were more likely to have impaired renal function. In multinomial logistic regression analyses with euthyroid participants as reference, transient SCH/overt hypothyroidism was independently associated with greater age and body mass index and anti-TPO positivity, while persistent SCH/overt hypothyroidism was associated with longer diabetes duration, anti-TPO positivity, and a lower frequency of antihypertensive medication use (see Table 2). In binomial logistic regression analysis with transient SCH/overt hypothyroidism as the reference group, persistent SCH/overt hypothyroidism was significantly associated with longer diabetes duration [odds ratio (95% confidence interval) 1.68 (1.08, 2.61); $P = .023$ for an increase of 5 years' duration].

Associations Between Thyroid Status and Changes in eGFR

There were no significant differences in the change in (Δ) eGFR, or in the proportion of subjects experiencing a >30% fall in eGFR, from baseline to follow-up between the 3 groups (see upper panel in Table 3). When categorized by baseline eGFR status (≥90 mL/min/1.73 m^2, 60-89 mL/min/1.73 m^2, and < 60 mL/min/1.73 m^2), there were similarly no statistically significant between-group differences.

Associations Between Thyroid Status and Changes in ACR

There was a significant increase in urine albumin excretion in those with persistent SCH/overt hypothyroidism compared to euthyroid participants (increase of 22.0 ± 81.4 mg/mmol vs 0.4 ± 35.9 mg/mmol; $P = .027$, see lower panel in Table 3), but this was not observed in those with transient SCH/overt hypothyroidism. This was also the case when participants with macroalbuminuria (ACR >30 mg/mmol) at baseline were excluded ($P < .001$; see Table 3). After stratifying the cohort for baseline albuminuria status, those with normal ACR at baseline showed more pronounced differences with a significant difference in mean ACR between the persistent hypothyroidism and euthyroid groups and a significant trend in the incidence of new-onset macroalbuminuria across the thyroid status categories (see Table 3). There were no significant differences in ΔACR between groups among those with microalbuminuria at baseline (see Table 3).

Associations Between Thyroid Status and Insulin Resistance

Relationships between persistent SCH/overt hypothyroidism vs euthyroidism and measures of insulin resistance were explored in analyses summarized in Table 4. There were no statistically significant associations between thyroid status and either eGDR or Homoeostasis Model Assessment Index of Insulin Resistance at baseline and, in the case of eGDR, its change over 4 years. There were similarly no associations between persistent SCH/overt hypothyroidism vs euthyroidism and either baseline or 4-year change in blood pressure measures.

Discussion

We found no evidence that persistent SCH/overt hypothyroidism was associated with an accelerated rate of loss of glomerular function over 4 years relative to that in either transient SCH/overt hypothyroidism or euthyroidism in people with type 2 diabetes, regardless of the degree of renal dysfunction at baseline. However, persistent SCH/overt hypothyroidism was associated with a significant increase in albuminuria over the follow-up period, especially in individuals with initially normal urinary albumin excretion. The present data provide evidence that this adverse effect on ACR was unlikely to have been mediated through either dysthyroid-related increased insulin resistance or hypertension. Although this suggests a direct pathophysiologic mechanism, the fact that there was no effect of transient SCH/overt hypothyroidism on ΔACR suggests that it is potentially reversible.

There are few longitudinal studies that have examined the temporal relationship between SCH and renal function. In a small cohort of hospital-based patients with stage 2 to 4 CKD (n = 168), persistent untreated SCH over 19.1 months was independently associated with a greater rate of renal function decline than in those in whom hypothyroidism resolved or who remained euthyroid (9). However, how patients were selected for assessment of thyroid status was not detailed, and the prevalence of SCH at baseline was very high (almost 25% of participants) relative to that in our community-based cohort. In a large Korean general population health screening program, baseline TSH was not independently associated with incident CKD (eGFR < 60 mL/min/1.73 m^2) in 104 633 participants free of CKD and proteinuria at baseline and who did not develop overt thyroid disease during follow-up (30). In the same study (30), there was a weak and modest positive relationship between time-varying TSH within the assay reference interval and incident CKD. How these findings relate to the present data in the context of type 2 diabetes is uncertain.

There are similarly few published studies of the association between thyroid disease and albuminuria. In 1 general population study, there was no independent association between SCH or overt hypothyroidism and prevalent proteinuria (2). However, in studies of individuals with diabetes and CKD, several have found this association to be significant (12-14).

Table 1. Baseline characteristics of people with type 2 diabetes by hypothyroidism status defined at baseline and year 4

	Euthyroidism	Transient subclinical/ overt hypothyroidism	Persistent subclinical/ overt hypothyroidism	*P*-value
n (%)	683 (91.1)	18 (2.4)	24 (3.2)	
Age (years)	64.3 ± 10.7	67.7 ± 7.7	69.2 ± 9.4	.036
Male (%)	60.6	44.4	66.7	.333
TSH (nmol/L)	2.1 (1.3-3.2)	6.0 (5.0-7.1)[a]	6.6 (5.4-8.2)[a]	<.001
FT4 (pmol/L)	15.4 (13.4-17.6)	13.8 (12.0-15.9)[b]	13.6 (12.2-15.2)[a]	<.001
Ethnic background (%):				.744
Anglo-Celt	55.1	61.1	41.7	
Southern European	12.6	16.7	8.3	
Other European	7.8	0	12.5	
Asian	5.1	5.6	4.2	
Aboriginal	4.0	0	8.3	
Mixed/other	15.5	16.7	25.0	
Not fluent in English (%)	9.2	11.1	8.3	.909
Education beyond primary level (%)	90.3	77.8	91.3	.222
Currently married/de facto relationship (%)	67.2	72.2	79.2	.474
Daily alcohol consumption (standard drinks of 10 U)	0.3 [0.0-1.5]	0.1 [0.0-0.4]	0.3 [0.0-1.2]	.118
Smoking status (%)				.806
Never	40.8	44.4	41.7	
Ex-	51.0	55.6	50.0	
Current	8.2	0	8.3	
ABSI ($m^{11/6}/kg^{2/3}$)	0.081 ± 0.005	0.081 ± 0.006	0.081 ± 0.005	.852
Body mass index (kg/m^2)	31.1 ± 5.5	33.9 ± 5.9	29.6 ± 5.3[c]	.043
Abdominal obesity (% by waist circumference)	69.5	88.9	54.2	.056
Age at diabetes diagnosis (years)	55.1 ± 11.5	61.1 ± 7.4	56.2 ± 10.7	.081
Diabetes duration (years)	7.9 [2.0-15.0]	4.5 [1.8-8.8]	13.8 [4.1-19.7]	.037
Diabetes treatment (%)				.592
Diet/exercise alone	26.7	33.3	16.7	
Oral hypoglycemic agents/noninsulin injectables	54.3	44.4	54.2	
Insulin ± oral hypoglycemic agents/noninsulin injectables	19.1	22.2	29.2	
Fasting serum glucose (mmol/L)	7.1 [6.2-8.7]	6.8 [5.9-7.9]	7.5 [6.4-9.0]	.436
HbA_{1c} (%)	6.8 [6.2-7.5]	6.4 [6.1-7.4]	7.3 [6.4-7.6]	.296
HbA_{1c} (mmol/mol)	51 [44-58]	46 [43-57]	56 [46-60]	.296
Systolic blood pressure (mmHg)	145 ± 21	153 ± 21	148 ± 16	.178
Diastolic blood pressure (mmHg)	81 ± 12	83 ± 13	79 ± 8	.533
Pulse rate (beats/min)	69 ± 12	73 ± 10	66 ± 6	.209
Antihypertensive medication (%)	74.0	66.7	50.0[d]	.035
ACE inhibitor/angiotensin receptor blocker use (%)	65.7	55.6	41.7	.038
Total serum cholesterol (mmol/L)	4.3 ± 1.1	4.1 ± 0.9	4.4 ± 0.9	.767
Serum HDL-cholesterol (mmol/L)	1.22 ± 0.32	1.28 ± 0.35	1.26 ± 0.37	.669
Serum triglycerides (mmol/L)	1.5 (0.9-2.4)	1.5 (1.0-2.2)	1.6 (1.1-2.4)	.667
Lipid-lowering medication (%)	71.2	72.2	66.7	.862
Aspirin use (%)	35.6	44.4	37.5	.691
Serum hsCRP (mg/L)	2.2 (0.7-6.4)	3.4 (0.9-12.4)	1.9 (0.6-6.3)	.193
Serum bicarbonate (mmol/L)	25 ± 2	24 ± 2	24 ± 2	.689
Plasma NT-proBNP (pmol/L)	56.8 (15.1-213.2)	119.3 (38.6-368.9)	55.0 (19.3-156.6)	.060
Serum albumin (g/L)	44.3 ± 2.7	44.6 ± 2.8	43.6 ± 2.6	.441
Serum gamma glutamyltransferase (U/L)	31 (13-72)	35 (15-78)	16 (1-211)[b,c]	.003
Serum uric acid (mmol/L)	0.34 ± 0.09	0.34 ± 0.07	0.34 ± 0.06	.978
Urinary albumin:creatinine ratio (mg/mmol)	2.8 (0.8-9.9)	2.9 (1.1-7.9)	1.7 (0.5-5.9)	.158
eGFR ($mL/min/1.73\ m^2$)	83.3 ± 18.2	80.4 ± 12.5	74.7 ± 19.8	.063

(*continued*)

Table 1. Continued

	Euthyroidism	Transient subclinical/ overt hypothyroidism	Persistent subclinical/ overt hypothyroidism	*P*-value
eGFR categories (%)			[d]	.004
≥90 mL/min/1.73 m^2	43.8	16.7	20.8	
60-89 mL/min/1.73 m^2	46.3	77.8	54.2	
<60 mL/min/1.73 m^2	9.8	5.6	25.0	
Any diabetic retinopathy (%)	34.7	33.3	45.8	.524
Peripheral sensory neuropathy (%)	56.8	61.1	45.8	.516
Peripheral arterial disease (%)	18.0	16.7	8.3	.581
Atrial fibrillation (%)	3.7	11.1	0	
Cerebrovascular disease (%)	7.0	16.7	4.2	.208
Coronary heart disease (%)	24.6	27.8	20.8	.882
Left ventricular hypertrophy (%)	1.6	0	4.2	.517
Heart failure (%)	3.1	0	0	
Anemia (%)	7.0	5.6	12.5	.427
Proton pump inhibitor use (%)	20.5	38.9	25.0	.146
Charlson Comorbidity Index (%)				.860
0	79.9	77.8	83.3	
1-2	15.1	16.7	8.3	
≥3	5.0	5.6	8.3	
Anti-TPO positivity (%)	5.0	22.2[d]	20.8[d]	<.001

Data are presented as mean ± SD, geometric mean (SD range), median [interquartile range]. All comparisons were adjusted for multiple comparisons using the Bonferroni correction.
Abbreviations: ABSI, A Body Shape Index; ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; FT4, free T4; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; anti-TPO, antibodies to thyroperoxidase.
[a] $P < .001$ vs euthyroid group.
[b] $P < .010$ vs euthyroid group.
[c] $P < .050$ vs transient hypothyroidism group.
[d] $P < .050$ vs euthyroid group.

Table 2. Multinomial logistic regression model of independent associates of hypothyroidism status defined at baseline and year 4 in people with type 2 diabetes (with euthyroid group as reference)

	Transient subclinical/ overt hypothyroidism	Persistent subclinical/ overt hypothyroidism
Age (increase of 10 years)	**1.85 (1.09, 3.14)**	1.59 (0.998, 2.54)
Diabetes duration (increase of 5 years)	0.76 (0.52, 1.11)	**1.29 (1.01, 1.64)**
BMI (increase of 1 kg/m^2)	**1.11 (1.03, 1.20)**	0.99 (0.91, 1.08)
On antihypertensive medication	0.51 (0.18, 1.49)	**0.23 (0.09, 0.57)**
TPO positive	**6.17 (1.84, 20.7)**	**5.63 (1.86, 17.0)**

Data are presented as odds ratios (95% confidence intervals). Figures in bold are those with a 95% confidence interval that does not include unity.
Abbreviations: BMI, body mass index; TPO, thyroid peroxidase.

In the only longitudinal study involving people with or without type 2 diabetes, baseline SCH was significantly associated with a small increase in albuminuria over a year (31). Our data suggest that more prolonged mild hypothyroidism, whether SCH or overt, may be a risk factor for clinically significant increases in ACR and the incidence of macroalbuminuria in people with type 2 diabetes, especially in those with normal ACR at baseline.

Two small trials of thyroid hormone replacement with renal end-points carried out in CKD and primary hypothyroid cohorts, respectively, found significant reductions in albuminuria (8, 16). Whether this applies in the case of type 2 diabetes is uncertain, but the fact that there was no effect of transient SCH/overt hypothyroidism on ΔACR in our participants suggests that thyroxine replacement may be beneficial in those with prolonged mild hypothyroidism. Of potential further support for replacement therapy is the observation that time with an abnormal TSH is positively associated with mortality in a laboratory database study and in hypothyroid patients on thyroxine (32-35).

It is unclear how persistent SCH/overt hypothyroidism influences urine albumin excretion. Recent studies have found an association between SCH/overt hypothyroidism and hypertension (18) as well as insulin resistance and components of the metabolic syndrome (17, 36), which are associated with increased urine albumin excretion (37). We found no associations between persistent SCH/overt hypothyroidism with change in blood pressure or insulin resistance, which suggests these factors are not mediators of the increase in albuminuria we observed in those with persistent hypothyroidism. However, in addition to evidence that SCH may accelerate endothelial dysfunction and its effects on ACR (38), there is preclinical evidence that low T3 levels associated with diabetes may lead to pathological changes in podocytes that promote proteinuria (39). Furthermore, animal in vivo studies and human in vitro experiments show that T3 administration can reverse these effects (40).

The present study had limitations. There was a relatively small number of participants with persistent SCH, especially

Table 3. Change in renal disease parameters over 4 years in people with type 2 diabetes categorized by thyroid status at baseline and year 4

	Euthyroidism	Transient subclinical/ overt hypothyroidism	Persistent subclinical/ overt hypothyroidism	*P*-value[a]
n (%)	681 (94.2)	18 (2.5)	24 (3.3)	
ΔeGFR (mL/min/1.73 m^2)	−7.1 ± 10.5	−4.5 ± 8.2	−6.7 ± 10.3	.553
% with eGFR decline >30%	7.0	5.6	16.7	.158
Baseline eGFR ≥90 mL/min/1.73 m^2 (n = 306)				
n (%)	289 (97.4)	3 (1.0)	5 (1.6)	
ΔeGFR (mL/min/1.73 m^2)	−5.6 ± 11.3	−4.1 ± 8.9	−7.1 ± 11.5	.738
% with eGFR decline >30%	3.0	0	0	>.999
Baseline eGFR 60-89 mL/min/1.73 m^2 (n = 343)				
n (%)	316 (92.1)	14 (4.1)	13 (3.8)	
ΔeGFR (mL/min/1.73 m^2)	−5.8 ± 11.4	−3.8 ± 9.1	−7.2 ± 11.1	.725
% with eGFR decline >30%	7.6	7.1	7.7	>.999
Baseline eGFR <60 mL/min/1.73 m^2 (n = 74)				
n (%)	67 (90.5)	1 (1.4)	6 (8.1)	
ΔeGFR (mL/min/1.73 m^2)	−4.9 ± 11.0	−8.7	−7.0 ± 13.3	.865
% with eGFR decline >30%	22.4	0	50.0	.361
n (%)	670 (91.1)	18 (2.4)	24 (3.2)	
ΔACR (mg/mmol; n = 712)	0.4 ± 36.7	−0.3 ± 5.7	22.0 ± 81.4*	.027
n (%)[b]	637 (93.8)	18 (2.7)	24 (3.5)	
ΔACR (mg/mmol; n = 679)[b]	3.2 ± 18.1	−0.3 ± 5.7	22.0 ± 81.4***,††	<.001
% with new-onset macroalbuminuria (n = 679)[b]	4.4	0	12.5	.162
Baseline ACR <3.0 mg/mmol (n = 456)				
n (%)	426 (93.4)	10 (2.2)	20 (4.4)	
ΔACR (mg/mmol)	1.2 ± 6.2	1.6 ± 3.8	23.4 ± 89.1***,†	<.001
% with new-onset macroalbuminuria	0.7	0	10.0	.021
Baseline ACR ≥3.0–<30.0 mg/mmol (n = 223)				
n (%)	211 (94.6)	8 (3.6)	4 (1.8)	
ΔACR (mg/mmol)	7.2 ± 29.7	−2.7 ± 7.1	14.9 ± 19.0	.553
% with new-onset macroalbuminuria	11.8	0	25.0	.411

Results for each group as a whole are shown together with categories of eGFR and ACR.
Abbreviations: ACR, albumin:creatinine ratio; eGFR, eGFR, estimated glomerular filtration rate.
[a]Unadjusted trend *P*-value.
[b]Excluding those with baseline macroalbuminuria
*$P < .05$ vs euthyroid, Bonferroni-adjusted for multiple comparisons; ***$P < .001$, vs euthyroid, Bonferroni-adjusted for multiple comparisons; †$P < .05$; ††$P < .01$ vs transient subclinical hypothyroidism/overt hypothyroidism, Bonferroni-adjusted for multiple comparisons.

Table 4. Changes in blood pressure and indices of insulin resistance over 4 years in people with type 2 diabetes with persistent subclinical/overt hypothyroidism vs euthyroid defined at baseline and year 4

	n	Euthyroidism	Persistent SCH/overt hypothyroidism	*P*-value	*P*-value[b]
n (%)		683 (96.6)	24 (3.4)		
Baseline eGDR (mg/kg/min)	706	4.9 ± 2.0	5.6 ± 2.2	.097	—
Ln(HOMA2-IR)[a]	567	1.74 (0.95-3.19)	1.94 (1.08-3.48)	.465	—
Baseline systolic blood pressure (mmHg)	706	145 ± 21	148 ± 16	.485	—
Baseline diastolic blood pressure (mmHg)	706	81 ± 12	79 ± 8	.341	—
ΔeGDR (mg/kg/min)	699	−0.04 ± 1.50	0.48 ± 1.70	.100	.272
Δsystolic blood pressure (mmHg)	703	4.6 ± 23.2	10.0 ± 23.0	.263	.381
Δdiastolic blood pressure (mmHg)	702	3.6 ± 13.6	6.2 ± 14.3	.354	.072

Data are presented as percentages, mean ± SD, geometric mean (SD range).
Change in variable (Δ) = value of variable at baseline − value of variable at follow-up.
Abbreviations: eGDR, estimated glucose disposal rate; HOMA2-IR, Homoeostasis Model Assessment Index of Insulin Resistance; SCH, subclinical hypothyroidism.
[a]In participants not on insulin.
[b]Adjusted for baseline value of variable using linear regression.

those with CKD and/or microalbuminuria, thus restricting multivariable analyses and increasing the chance of a false-negative observation. This included assessment of the potential effect of categorical changes in glycemic control and renin-angiotensin blocking medication use by thyroid function status on ΔACR, with low single-figure numbers in some subgroups. We cannot exclude the possibility of reverse causality, specifically that a persistent increase in TSH is a result of worse renal function or other comorbidities. As eligible participants were those who remained in the study for 4 years, the results may not be generalizable to all people with type 2 diabetes. However, our results were statistically significant after careful adjustment for multiple comparisons, and we were able to investigate potential confounders in bivariable analyses.

In conclusion, we found that, in this well-characterized cohort of people with type 2 diabetes, persistent SCH/mild overt hypothyroidism was associated with a marked increase in albuminuria that was not observed in euthyroid participants or those with transient hypothyroidism. Further studies of this association are warranted to identify mediating factors. People with long-standing type 2 diabetes may benefit from regular monitoring of their thyroid function, in contrast to recommendations from guidelines (20), as prior published evidence suggests that thyroid replacement may have a role in ameliorating albuminuria and its sequelae.

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Disclosures

No conflicts of interest to declare.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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