Association between subclinical hypothyroidism and diabetic nephropathy in type 2 diabetes

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Introduction
Diabetes mellitus and thyroid dysfunction are two endocrine disorders that can affect each other, and the effects of which are poorly understood until now. Association between subclinical hypothyroidism (SCH) and diabetic nephropathy (DN) remains unclear.
Aim
The aim was to evaluate the association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus (T2DM).
Patients and methods
A total of 242 patients with type 2 diabetes were recruited in the study who, according to the results, were subdivided into three groups: euthyroid group [thyroid stimulating hormone (TSH) 0.30–4.2 mIU/ml], SCH group (TSH >4.2 and < 10 mIU/ml) with negative antithyroid peroxidase antibodies (anti-TPO), and SCH group with positive anti-TPO.
Results
Our study shows a high prevalence of subclinical hypothyroidism (29.8%) and DN (47.1%) among type 2 diabetic patients. SCH predicted diabetic nephropathy with an odd ratio of 1.86 (1.01–3.41) and *P* value of 0.03. There is a significant positive correlation between albuminuria with TSH ($P< 0.001$), and there is a significant positive correlation between albuminuria with anti-TPO ($P< 0.001$). Moreover, there are significant inverse correlations between glomerular filtration rate (GFR) with TSH ($P<0.05$) and between GFR and anti-TPO ($P< 0.001$).
Conclusion and recommendation
There is an association between subclinical hypothyroidism and diabetic nephropathy in T2DM. Regular testing of the thyroid function is recommended for all patients with T2DM to avoid DN or more deterioration of the kidney functions. Future larger studies are needed to know the exact mechanism by which high serum TSH leads to renal impairment and for evaluating the proper TSH target in patients with T2DM.

Keywords:
diabetic nephropathy, subclinical hypothyroidism, type 2 diabetes mellitus

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Introduction

Diabetic nephropathy is the first cause of renal insult around the world, and it is significantly related to high morbidity and mortality. Approximately 20–40% of patients with type 2 diabetes will develop diabetic nephropathy (DN) and 40% of patients with DN will progress to end-stage renal disease [1].

Diabetic kidney disease is considered one of the most frequent complications of type 2 diabetes mellitus (T2DM) [2]. The diagnosis of diabetic nephropathy is considered according to the National Kidney Foundation classification, which is based on kidney damage [spot urinary albumin/creatinine ratio (UACR) ≥30 mg/g with reduced estimated glomerular filtration rate (eGFR) <60 ml/min./1.73 m^2] [3]. The American Diabetes Association recommends screening for albuminuria at the time of T2DM diagnosis, this considered as diabetic patients might not recognized for years [4].

Recent studies reported a higher prevalence of subclinical hypothyroidism (SCH) in patients with T2DM than euglycemic population and higher prevalence of SCH among patients with T2DM with nephropathy than diabetics with intact renal functions [5]. However, the clinical effects of these recent studies are still not well known as to whether SCH is related to diabetes control or considered as late

diabetic complications in all patients with T2DM [6]. There are many interactions between SCH and kidney functions; thyroid hormone affects renal development and physiology, has pre-renal and renal effects, and can increase the renal blood flow leading to reduced GFR. So hypothyroidism may result in reduced GFR, and hyperthyroidism is associated with increased GFR as well as excited system of renin–angiotensin–aldosterone [7].

CKD is characterized by a low T3 syndrome, which is considered as a part of atypical nonthyroidal illness. Patients with CKD can be associated with primary hypothyroidism and SCH. Autoimmune thyroid dysfunction is associated with glomerulonephritis often by a common autoimmunity. Moreover, several drugs could affect both thyroid and kidney functions [8].

The serum thyroid stimulating hormone (TSH) level has been reported to be an independent risk factor of albuminuria [7]. Association between SCH and the risk of CKD is still a matter of debate [8].

Hypothyroidism has been related to a few key effects on insulin secretion and glucose levels. In contrast to hyperthyroidism, hypothyroidism reduces glucose absorption from the intestine. It is also associated with an almost complete cessation of hepatic glucose output and an increase in serum insulin levels [9].

Homeostasis model assessment insulin resistance (HOMA-IR) values were reported higher in subjects with subclinical hypothyroidism than in euthyroid subjects, suggesting that low thyroid hormone will lead to insulin resistance [10]. Moreover, TSH was positively correlated with insulin and HOMA-IR values, whereas FT4 and FT3 were inversely correlated with insulin and HOMA-IR [9].

The aim of the present work was to evaluate the association between subclinical hypothyroidism and diabetic nephropathy in patients with T2DM.

Patients and methods

The protocol of this study was approved by the local ethics committee in March 2017. The authors have no conflicts of interest, and they alone are responsible for the content and writing of the paper. This study was carried out on 242 subjects. After being informed on the purpose and procedures of the study, all subjects signed on an informed consent form. Our subjects included 242 type 2 diabetic patients aged from 45 to 84 years old who were subdivided to three groups: group 1, euthyroid group (TSH 0.30–4.2); group 2a, SCH (TSH >4.2 and < 10) with negative antithyroid peroxidase antibodies (anti-TPO), and group 2b, SCH with positive anti-TPO. The patients included in our study were older than 18 years with type 2 diabetes. The diagnosis of type 2 diabetes was confirmed by the American Diabetic Association criteria: fasting plasma glucose (FBS) level of greater than or equal to 126 mg/dl (repeated testing should confirm the result) or 2-h postprandial plasma glucose level of greater than or equal to 200 mg/dl or A1C greater than or equal to 6.5% or classic symptoms of diabetes in addition to random plasma glucose greater than or equal to 200 mg/dl and uncontrolled DM with HBA1c greater than or equal to 7 [4]. The nondiabetic patients, type 1 diabetics, patients with history of thyroid disease, patients with end-stage renal failure, patients with acute liver disease, patients with acute or severe illness, and patients receiving any drugs that affect thyroid functions (e.g. metformin, anti-thyroid drugs, and cortisone) or affect albuminuria all were excluded from our study.

Patient evaluation

Patient evaluation was done through history taking. A detailed history with stress on age of onset of diabetes, the presence of any associated thyroid illness, and the presence of any associated autoimmune disease was obtained. Additionally, a history of insulin intake or antidiabetic drugs was properly taken, a history of presence of any associated renal illness or end-stage renal failure, and physical examination with stress on anthropometric measures (weight and BMI) were assessed. BMI was measured by calculation of weight by kilogram/length by square meter [11]. Systemic examination was done searching for any signs of thyroid disease, other autoimmune stigmata as vitiligo, myasthenia graves or rheumatoid arthritis and any renal disease or severe illness.

Investigations

Lipid profile, HBA1c, fasting glucose, 2-h PP glucose, measurement of TSH (normal range: 0.30–4.2 mIU/ml, using ADVIA Centaur CP Immunoassay System; By GMI 6511 Bunker Lake BoulevardRamsey, MN 55303, United States), anti-TPO antibody (Normal range: up to 34 IU/ml, using Cobas e 411 Apparatus; By Roche Diagnostics GmbH, D-68298 Mannheim, Germany), and eGFR (nephropathy if reduced GFR<60 ml/min/1.73 m^2) [3,12] were examine. The determination of eGFR was done by the following equation: MDRD eGFR=186×[plasma creatinine (μmol/l)×0.0011312]−1.154×[age

(years)]−0.203×(0.742 if female)×(1.212 if African American) [13]. Albumin/creatinine ratio in urine was also calculated (nephropathy may be macroalbuminuria if albumin is ≥300 mg/g creatinine on at least two out of three tests done 3 months apart or microalbuminuria if albumin is 30–300 mg/g creatinine) [14].

Statistical methods

Data were entered checked and analyzed using Epi-Info version 6 [Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, US] and SPP for Windows version 8 (Microsoft, Redmond, Washington, US). Baseline characteristics of the study population were presented as frequencies and percentages or mean values and SD. Analysis of variance test was used to analyze repeated measures. Differences between two quantitative variables were compared by Student's *t*-test. Correlation of numeric data was done by Pearson's correlation (*r*). Five percent probability is adopted as the level of statistical significance in all statistical tests ($P<0.05$), and ($P<0.001$) was considered as highly significant.

Results

Table 1 shows the baseline characteristics of the study population: HbA1c (%) ranged from 5.8 to 11, with mean+SD of 7.6±1.3. Age (years) ranged from 45 to 84, with mean+SD of 58.9±7.3. BMI (kg/m^2) ranged from 24 to 35.5, with mean±SD of 30.75±2.9. FBS (mg/dl) ranged from 95 to 210, with mean+SD of 140.99±33.1. The 2-h post-prandial glucose (mg/dl) ranged from 129 to 333, with mean±SD of 209±53.1. TG (mg/dl) ranged from 75 to 201, with mean±SD of 125.8±41.9. Total cholesterol (mg/dl) ranged from 78 to 276, with mean±SD of 165.6±54.6. TSH (mIU/l) ranged from 0.01 to 7.1, with mean±SD of 3.4±2.2. Albuminuria (mg/g creatinine) ranged from 3 to 701, with mean±SD of 118.3±171.3. eGFR (ml/min/1.73 m^2) ranged from 15 to 160, with mean±SD (73.1±40.9). Anti-TPO (IU/ml) ranged from 9 to 63, with mean±SD of 18.9±13.1.

Table 2 shows the prevalence of subclinical hypothyroidism in our patients. This table shows that 242 type 2 diabetic patients were included as follows: 170 (70.2%) patients were euthyroid negative anti-TPO and 72 patients (29.8%) were SCH [24 (9.9%) patients with positive anti-TPO and 48 (19.8%) patients with negative anti-TPO]. The total number of patients with positive anti-TPO was 24 (9.9%), but the total number of patients with negative anti-TPO was 218 (90.1%).

Table 3 shows the comparisons between all groups regarding variables between euthyroid and subclinical hypothyroidism with negative or positive anti-TPO using analysis of variance. This table shows that there is a highly statistically significant difference between groups regarding microalbumin/creatinine ratio in urine ($P<$ 0.001), with a higher value in group 2b (SCH with positive anti-TPO), with mean±SD of 372.4±210 and range from 189 to 701, in comparison with the other two groups, as in group 1, mean±SD was 67.4±109 and in group 2a was 171.7 ±204. Moreover, this table shows that there is a highly statistically significant difference between groups regarding GFR ($P<$ 0.001) and the least value was in group 2b, with mean±SD of 30.6±15.6 and range from 15–45, in comparison with the other two groups, as in group 1 mean±SD was 82.1±39.7 and in group 2a

Table 1 Baseline characteristics for the study population (mean, SD, minimum, and maximum)

Variable	Mean	SD	Minimum	Maximum
HbA1c	7.6	1.3	5.8	11
Age (years)	58.9	7.3	45	84
BMI (kg/m^2)	30.75	2.9	24	35.5
Fasting plasma glucose (mg/dl)	140.99	33.1	95	210
2-h postprandial glucose (mg/dl)	209	53.1	129	333
TG (mg/dl)	125.8	41.9	75	201
Total cholesterol (mg/dl)	165.6	54.6	78	276
TSH (mIU/l)	3.4	2.2	0.01	7.1
Albuminuria (mg/g creatinine)	118.3	171.3	3	701
eGFR (ml/min/1.7 3 m^2)	73.1	40.9	15	160
Anti-TPO (IU/ml)	18.9	13.1	9	63
DM duration	11.9	3.5	6.6	20.5

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; TG, triglycerides; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Table 2 Prevalence of subclinical hypothyroidism

Variables	Result	*n* (%)
Thyroid function in type 2 diabetes	(1) Euthyroid (TSH <4.2)	170 (70.2)
	SCH (TSH >4.2)	72 (29.8)
Anti-TPO in type 2 diabetes	(2) Anti-TPO	
	Negative	218 (90.1)
	Positive	24 (9.9)
Anti-TPO in SCH	(2a) SCH with negative anti-TPO	48 (66.7)
	(2-b) SCH with positive anti-TPO	24 (33.3)

SCH, subclinical hypothyroidism; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Table 3 Comparisons between all groups regarding variables between euthyroid and subclinical hypothyroidism with negative or positive antithyroid peroxidase using analysis of variance

Variables	1 (*N*=170) (mean±SD)	2a (*N*=48) (mean±SD)	2b (*N*=24) (mean±SD)	*F*	*P* value
Albuminuria					
Mean±SD	67.4±109	171.7±204	372.4±210	25.5	<0.001
Range	3–701	13–601	189–701		
eGFR					
Mean±SD	82.1±39.7	62.9±38.8	30.6±15.6	10.8	<0.001
Range	17–160	16–145	15–45		
Age (years)	59.5±5.7	57.9±8.9	56.1±7.7	1.4	NS
DM duration	12.7±3.3	11.3±5.5	11.8±4.75	1.2	NS
BMI (kg/m^2)	30.4±2.9	30±2.1	30.6±3.2	0.09	NS
Sex [*n* (%)]					
Male	144 (84.7)	40 (83.3)	24 (100)	χ^2=2.2	NS
Female	26 (15.3)	8 (16.7)	0 (0)		

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

Table 4 Between-group comparisons of the variables by mean±SD between patients with normal urine protein excretion and diabetic nephropathy

Variables	Normal protein (*N*=64)		Nephropathy (*N*=57)		*P* value
	Mean	SD	Mean	SD	
Age (years)	59.2	8.1	58.5	6.5	NS
T2DM duration	3.7	2.1	16.4	4.5	<0.001
BMI (kg/m^2)	30.4	3.1	30.3	2.5	NS
Fasting plasma glucose (mg/dl)	120.3	16.9	164.2	31.3	<0.001
2-h postprandial glucose (mg/dl)	176.6	24	245.4	53	<0.001
HbA1c (%)	6.9	1.0	8.4	1.1	<0.001
TG (mg/dl)	102.2	21.7	152.2	43.8	<0.001
Total cholesterol (mg/dl)	137.9	44	196.6	47.9	<0.001
TSH (mIU/l)	3.0	1.8	3.9	2.3	0.028

T2DM, type 2 diabetes mellitus; TG, triglycerides; TSH, thyroid stimulating hormone.

was 62.9±38.8. Or else, no statistically significant difference was found between groups regarding age, DM duration, BMI, and sex.

Table 4 reveals between-group comparisons of the variables between subjects with normal urine protein excretion and diabetic nephropathy. This table shows a highly statistically significant difference between groups regarding duration of T2DM by years ($P<$ 0.001), which is higher in nephropathy group, with mean+SD of 16.4±4.6 years, compared with the normal urine protein group, with mean+SD of 3.7±2.1. FBS (mg/dl) ($P<$ 0.001) is higher in nephropathy group, with mean±SD of 164.2±31.3 compared with the normal urine protein group. The 2-h postprandial glucose (mg/dl) is higher also in nephropathy group (176.6±24) in comparison with normal urine protein group (245.4±53), with significant *P* value of less than 0.001. Regarding HbA1c, higher readings were recorded in nephropathy group (8.4±1.1) than in normal urine protein group (6.9±1.0) ($P<$ 0.001). The table also shows a highly statistically significance difference between groups regarding TG and total cholesterol (mg/dl) ($P<$ 0.001), as mean±SD in nephropathy group was 152.2±43.8 and 196.6±47.9, respectively, which is higher than in normal urine protein group, at 102.2±21.7 and 137.9±44, respectively.

Regarding the TSH values, there are higher levels in nephropathy group (TSH=3.9±2.3) than in normal urine protein group (TSH 3.0±1.8), with statistically significance difference ($P=$ 0.028). However, our results show no statistically significance difference between groups regarding age or BMI.

Table 5 reveals the association between SCH and other factors. There was a significant difference between groups regarding incidence of the albuminuria ($P<$ 0.001). The highest incidence was in group 2b (SCH with positive anti-TPO), with 24 (100%) patients having albuminuria, in comparison with group 2a and group 1, which had 19(39.6%) and 38 (22.4%) patients, respectively. There was a significant difference between groups regarding incidence of patients with low e GFR (<60 ml/min./1.73 m^2) ($P<$ 0.001); the highest incidence was in group 2b, with 24 (100%) patients, in comparison with group 2a

Table 5 Association between subclinical hypothyroidism and other factors

Factors	1 (*N*=170) (*n*/%)	2a (*N*=48) (*n*/%)	2b (*N*=24) (*n*/%)	χ^2	*P*
Hypertension	(52/30.6)	(15/31.3)	(9/37.5)	0.47	NS
Dyslipidemia	(60/35.3)	(21/43.8)	(10/41.7)	1.33	NS
HBA1c≥7	(63/37)	(20/41.7)	(11/45.8)	0.88	NS
Albuminuria	(38/22.4)	(19/39.6)	(24/100)	57.9	<0.001
eGFR<60	(27/15.9)	(16/33)	(24/100)	75.2	<0.001

eGFR, estimated glomerular filtration rate.

Table 6 Multivariate analysis for factors predicting diabetic nephropathy

Factors	Odd ratio (95% confidence interval)	*P*
DM duration	4.0 (2.04–7.88)	<0.001
HBA1c	3.0 (1.58–5.72)	<0.001
SCH	1.86 (1.01–3.41)	0.03

DM, diabetes mellitus; SCH, subclinical hypothyroidism.

and group 1, which had 16 (33%) and 27 (15.9%), respectively. On the contrary, our results did not demonstrate significant difference ($P>0.05$) between groups regarding the incidence of other predicting factors for nephropathy such as hypertension, dyslipidemia, or uncontrolled DM (HBA1c≥7).

Table 6 shows the multivariate analysis for factors predicting diabetic nephropathy. The factors that add significance to the model and predict diabetic nephropathy were as follows: duration of DM with odds ratio of 4 (2.4–7.88) and *P* value of less than 0.001, then HBA1c, with odds ratio of 3 (1.58–5.72) and *P* value of <0.001, and also SCH, with odd ratio of 1.86 (1.01–3.41) and *P* value of 0.03.

Table 7 reveals a high significant positive correlation ($P< 0.001$) between albuminuria and TSH, a high significant positive correlation ($P< 0.001$) between albuminuria and anti-TPO, a significant inverse correlation ($P<0.05$) between GFR and TSH, and a high significant inverse correlation between GFR and anti-TPO.

Discussion

In our cross-sectional study, we entailed an association between subclinical hypothyroidism and diabetic nephropathy in purely type 2 diabetic patients who did not have symptoms or signs of hypothyroidism and DN. We found an association between subclinical hypothyroidism and diabetic nephropathy in T2DM. We observed albuminuria in patients with abnormal TSH and anti-TPO, with inverse correlation between GFR and TSH as well as anti-TPO.

Table 7 Correlation between thyroid stimulating hormone and antithyroid peroxidase with diabetic nephropathy

Nephropathy	*r*/*P*	TSH	Anti-TPO
Albuminuria	*r*	0.31	0.53
	P	<0.001	<0.001
GFR	*r*	–0.21	–0.4
	P	<0.05	<0.001

GFR, glomerular filtration rate; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Thyroid dysfunction is known to be more prevalent in T2DM compared with the general euglycemic populations. Type 2 diabetics are not usually screened for thyroid dysfunction on recent diagnosis [15].

The hyperglycemia in diabetics can affect thyroid capacity, bloating the pituitary TSH response to stimulation by hypothalamic TRH. This is because of the possible effect of post-translational glycosylation in TRH, thus altering the biological activity. So we can state that diabetes may incline to thyroid dysfunction. However, both hyperthyroid and hypothyroid states are known to have effects on glycemic control in T2DM [16].

In our study, the mean BMI ranged from 24 to 35.5 kg/m^2 with mean±SD of 30.75±2.9 in type 2 diabetic patients. Our results are in agreement with Kubo *et al.* [17] whose conducted a study on type 2 diabetic patients with mean BMI of 34.4±9 kg/m^2, and they relate this to chronic hyperglycemia associated with diabetes, which leads to increased fatty tissue and BMI [6]. Concerning the glycemic control in our studied groups, the FBS ranged from 95 to 210 mg/dl with mean±SD of 140.99±33.1 in type 2 diabetic patients. Mansournia *et al.* [16] supported our results as the FBS ranged from 63 to 469 with mean±SD of 147±51.8 in their type 2 diabetic patients, and they owed this to improper control of diabetes of the sample of patients used in the research. On the contrary, the findings of Kimmel *et al.* [6] did not coincided with our results because of tight control of the sample used in their research because of hospitalization.

Moreover, 2-h postprandial glucose ranged from 129 to 333 mg/dl with mean±SD of 209±53.1 in type 2 diabetic patients. This result is in agreement also with Mansourni *et al.* [16] in which the 2-h postprandial glucose ranged from 84 to 935 mg/dl with mean±SD of 233.3±98.4 in type 2 diabetic patients, and they owed this to improper control of diabetes of the sample of patients used in the research. The findings of Kimmel *et al.* [6] were not in agreement with our results because of tight control of blood glucose of the sample used in the research and also because of their hospitalization.

Our results showed that TG ranged from 75 to 201 mg/dl and total cholesterol ranged from 78 to 276 mg/dl in type 2 diabetes. Similar results were confirmed by Tangvarasittichai *et al.* [18] who found that TG ranged from 91 to 198 mg/dl and total cholesterol ranged from 164 to 208 mg/dl in type 2 diabetes and they explained this by chronic hyperglycemia which leads to increased dyslipidemia. On the contrary, the results of Anavekar *et al.* [19] did not coincided with ours, as they used anti-dyslipidemic drugs in a wide number of their patients. In this study, we found that albuminuria ranged from 3 to 701 (mg/g creatinine) with mean±SD of 118.3±171.3 in type 2 diabetes. The results of Tangvarasittichai *et al.* [18] were against our results as albuminuria ranged from 34.8 to 287.2 (mg/g creatinine), with mean of 79.4 in type 2 diabetes, and this may be related to the younger age of the sample size they used in the research, so hyperglycemia is more chronic in our patients than them leading to advanced albuminuria.

Regarding our results for TSH in type 2 diabetes, TSH ranged from 0.01 to 7.1 mIU/l with mean±SD of 3.4 ±2.2, which is contrary to Mansournia *et al.* [16] who found TSH in their patients with type 2 diabetes, which ranged from 0.1 to 9.5 with mean±SD of 2.5 ±1.8, and this difference can be explained by the bigger sample size they used.

In our study, the prevalence of SCH is 29.8% among type 2 diabetic patients, which is similar to the results confirmed by Vijayalakshmi *et al.* [20] as they reported 18% prevalence of SCH in T2DM; Mansournia *et al.* [16] with 18.1 prevalence of SCH in T2DM; and Ghada *et al.* [21], with SCH prevalence was 19.1% in T2DM. This high prevalence of SCH could be related to the improper control of diabetes, especially in the sample of patients used in the research. However, in the study by Shinya *et al.* [22] the prevalence of SCH was 8.7% among patients with T2DM, which could be related to wide sample size (512 population) and to good control of diabetes, as HbA1c and fasting and post prandial sugar levels were convenient compared with the bad control of our studied patients.

We found that there was a high significant difference between the SCH and euthyroid groups regarding albuminuria and eGFR, and SCH is a predicting risk factor for diabetic nephropathy. In agreement with our findings, Tangvarasittichai *et al.* [18] explained this to increased reduction of GFR in SCH than euthyroid patients, but Hadjadj *et al.* [23] reported against our results, as they stated that there is no significant difference between groups regarding albuminuria and eGFR, and this can be owing to their use of nondiabetic patients in their sample size with less chronic hyperglycemia, less SCH, and less diabetic nephropathy.

We concluded that there is a high significant positive correlation between albuminuria and TSH and a high significant positive correlation between albuminuria and anti-TPO. In agreement with our results, Shinya *et al.* [22] and El-Eshmawy *et al.* [24] detected a significant positive correlation between albuminuria and TSH, and they stated that SCH was associated with the presence of diabetic nephropathy among patients with T2DM owing to the higher presence of dyslipidemia and vascular affection in SCH than diabetics without SCH.

Mansournia *et al.* [16] also reported similar to our results as they reported significant positive correlation between albuminuria and TSH and they explained this by high low cardiac output and vascular resistance, which are vascular consequences of hypothyroidism, and both may be the underlying causes of diminished renal blood flow then reduced GFR and albuminuria. Moreover, they owed this to thick basement membrane in the endothelium of precapillary and capillary arterioles and an inverse relationship between eGFR and TSH owing to atherosclerosis occurring in hypothyroidism by increasing total cholesterol and LDL-C lipoprotein, which in turn leads to cardiac and renal impairment.

Similarly, Zhang *et al.* [25] suggested SCH as a risk factor for albuminuria, and they explained this to renal function, which is influenced by thyroid status; the effects of thyroid dysfunction on the kidney include changes in renal blood flow, GFR, tubular secretory and absorptive capacity, electrolyte pumps, and kidney structure, leading to increased protein passage across renal glomeruli.

In contrary to our results, Muchta *et al.* [26], did not find any correlation between albuminuria and TSH, and this may be related to no sufficient parameters of their study as they did not study anti-TPO or GFR. However, Zhou *et al.* [8] reported similar findings to our results as they reported significant a positive correlation between albuminuria and anti-TPO and explained this by autoimmune mechanisms which occur at the level of thyroid leading to SCH and at the level of kidney leading to diabetic nephropathy.Our results were also confirmed by Kimmel *et al.* [6] as they stated that the GFR is reversibly reduced (by about 40%) in more than 55% of adults with hypothyroidism

owing to several reasons. There is less sensitivity to β-adrenergic receptors and diminished renin release, with decreased angiotensin-II and decreased RAAS activity, resulting in low GFR. There is also a structural constraint owing to limited glomerular surface area, leading to less filtration by renal parenchymal growth retardation in hypothyroidism.

The results of Sanai *et al.* [27] are in agreement with our results, as they reported high significant inverse correlation between GFR and anti-TPO, and they stated that multiple contributing variables have been proposed for this effect, including altered iodine metabolism and autoimmune thyroiditis which is more occurring in diabetic nephropathy patients than normal ones because of associated immune mechanisms in both SCH and nephropathy.

Zhou *et al.* [8] also reported similar findings to our results, as they found that GFR in patients with SCH is lower than that in euthyroid individuals. It is known that autoimmune thyroid disease can lead to the deposition of immune-complexes in renal glomeruli.

In our results, there is a significant inverse correlation ($P< 0.05$) between GFR and TSH, and there is a high significant inverse correlation between GFR and anti-TPO. Many mechanisms can explain this, but deposition of TPO antibodies with formation of glomerular immunocomplexes and altered immune tolerance for megalin (a thyrotropin-regulated glycoprotein) expressed on thyroid cells are the most probable mechanisms, as well as cross-reactivity between antigens with genetic predisposition [28].

Muchta *et al.* [26] reported contrary to our results, as they could not find any correlation between GFR and TSH, and this can be explained by their small sample size and inclusion of non-diabetics in it.

In contrast, Yasuda *et al.* [29] did not support our results, and they owed this to disorders of thyroid function which have been linked to the development of immune-mediated glomerular injury which not clear, and we can relate this to their utilization of nonsufficient parameters.

There are several limitations to the interpretation of our data. The cross-sectional nature of the study prevented us from inferring a causal relationship and also the small number of studied patients.

Conclusion and recommendations

The present evidence suggested that SCH could be a significant risk factor for CKD in T2DM. There is an association between subclinical hypothyroidism and diabetic nephropathy in T2DM. Regular testing of the thyroid function is recommended for all patients with T2DM to avoid DN or more deterioration of the kidney functions. Future larger studies are needed to know the exact mechanism by which high serum TSH leads to renal impairment and to evaluate the proper TSH target in patients with T2DM.

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Conflicts of interest

There are no conflicts of interest.

References

1 Bell G, Pennisi M, Monitini L, Silva S, Maviglia R, Cavallaro F, *et al.* Non thyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. Chest 2002; 135:1448–1454.

2 US Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013.

3 Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, *et al.* Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD guidline update). Kidney Int 2017; 92:26–36.

4 Chamberlain JJ, Rhinehart A, Shaefer CF Jr, Neuman A. Diagnosis and Management of Diabetes: Synopsis of the2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Int Med 2016; 164:542–554.

5 Chen HS, Wu TE, Jap TS, Lu RA, Wang ML, Chen RL, *et al.* Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in type 2 diabetic patients. Diabet Med 2007; 24:1336–1344.

6 Kimmel M, Braun N, Alscher M. Influence of thyroid function on different kidney function tests. Kidney Blood Press Res 2012; 35:9–17.

7 Radaideh R, Nusier MK, Amari FL, Bateiha AE, El-Khateeb MS, Naser AS, *et al.* Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. Saudi Med J 2013; 25:1046–1050.

8 Hong-Bing Li, Xiao-Rong Zhu, Hai-Lin Song, Ying-Ying Zhao, Jin-Kui Yang, *et al.* Subclinical hypothyroidism and the risk of chronic kidney disease in T2D subjects. Medicine 2017; 96:e6519.

9 Arnould M, Rashidi M, Shojaoddiny A. Effect of thyroid dysfunction on metabolic response in type 2 diabetic patients. Iran J Diabetes Obes 2011; 2:20–26.

10 Erdogan S, Garg S, Frias J, Maggs D, Wang Y, Zhang B, *et al.* A double blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care 2013; 4:1–7.

11 Johansson E, Kanis JA, Odén A, McCloskey E, Chapurlat RD, Christiansen C, *et al.* A meta-analysis of the association of fracture risk and body mass index in women. J Bone Mineral Res 2014; 29:223–233.

12 Bakris G. Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus. Mayo Clin Proc 2011; 86:444–456.

13 Florkowski C, Harris J. Methods of estimating GFR – different (2016) equations including CKD-EPI. Clin Biochem Rev 2011; 32:75.

14 Perkins BA, Ficoclello LH, Roshan B, Warram JH, Krolewski AS. In patients with type 1 diabetes and new-onset micro-albuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. Kidney Int 2010; 77:57–64.

15 Robin Maskey, Dhana Ratna Shakya, Jouslin Kishore Baranwal, Poonam Lavaju, Prahlad Karki, Shyam Krishna Poudel, *et al.* Profile of the thyroid function in a population with type 2 diabetes mellitus. Endocr Abstracts 2016; 3:298.

16 Mansournia N, Riyahi S, Tofangchiha S, Mansournia MA, Riahi M, Heidari Z, Hazrati E. Subclinical hypothyroidism and diabetic nephropathy in Iranian patients with type 2 diabetes. J Endocrinol Invest 2017; 40:289–295.

17 Kubo A, Ferrara A, Laurent CA, Windham GC, Greenspan LC, Deardorff J, *et al.* Associations between maternal pre gravid obesity and gestational diabetes and the timing of pubarche in daughters. Am J Epidemiol 2016; 184:7–14.

18 Tangvarasittichai S, Tangvarasittichai O, Meemark S. Estimated creatinine clearance and micro-albumin levels for early prediction of nephropathy in adults with diabetes mellitus. Siriraj Med J (Original Article) 2015; 4:204–205.

19 Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, *et al.* Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2015; 351:1285–1295.

20 Vijayalakshmi M, Mahalakshmi R, Shanthi R. Prevalence of sub-clinical hypo-thyroidism in type 2 diabetes mellitus. Stanley Med J 2016; 3:1–10.

21 Ghada A, Amira E. Subclinical hypothyroidism ups the risk of vascular complications in type 2 diabetes. Alexandria J Med 2016; 53:1–4.

22 Shinya F, Yamamoto S, Todo Y, Maruyama K, Miyake T, Ueda T, *et al.* Association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus. Endoc J 2014; 61:1011–1018.

23 Hadjadj S, Cariou B, Fumeron F, Gand E, Charpentier G, Roussel R, *et al.* Death, end-stage renal disease and renal function decline in patients with diabetic nephropathy in French cohorts of type 1 and type 2 diabetes. Diabetologia 2017 59: 208–216.

24 El-Eshmawy M, Abd El-Hafez HA, El Shabrawy WO, Abdel Aal IA. Subclinical hypothyroidism is independently associated with micro-albuminuria in a cohort of pre diabetic Egyptian adults. Diabetes Metab J 2016; 37:450–457.

25 Zhang A, Williams P. The thyroid and pregnancy: a novel risk factor for very preterm delivery. Thyroid 2016; 15:351–357.

26 Muchta E, Dean DS, Dispenzieri1 A, Dingli D, Buadi FK, Lacy MQ, *et al.* Prevalence and predictors of thyroid function abnormalities in newly diagnosed AL amyloidosis. J Intern Med 2017; 281:611–619.

27 Sanai T, Okamura K, Kishi T, Miyazono M, Ikeda Y, Kitazono T. Importance of specific reference values for evaluation of the deteriorating thyroid function in patients with end-stage renal disease on hemodialysis. J Endocrinol Invest 2015; 38:47–56.

28 Domenico S, Carmela V, Rosella S, Michele B, Salvatore B. Autoimmune thyroiditis and glomerulopathy. Front Endocrinol Lausanne 2017; 8:119.

29 Yasuda T, Kaneto H, Kuroda A, Yamamoto T, Takahara M, Naka T, Miyashita K. Subclinical hypothyroidism is independently associated with albuminuria in people with type 2 diabetes. Diabetes Res Clin Pract 2016; 94:75–77.