An Association Between Subclinical Hypothyroidism and Sight-Threatening Diabetic Retinopathy in Type 2 Diabetic Patients

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OBJECTIVE — To determine the relationship between subclinical hypothyroidism (SCH) and the prevalence of diabetic retinopathy in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 1,170 type 2 diabetic patients were screened for thyroid function. There were 127 type 2 diabetic patients with SCH and 200 randomly selected euthyroid type 2 diabetic patients selected. Those with more severe than moderate nonproliferative diabetic retinopathy were classified as having sight-threatening diabetic retinopathy (STDR).

RESULTS — The trend for severe retinopathy was significantly higher in the SCH group than in the euthyroid group ($\chi^2 = 20.43$, $P = 0.000$). SCH was associated with greater prevalence of diabetic retinopathy, especially STDR [odds ratio (95% CI): 4.15 (2.17–7.96), $P = 0.000$] after an adjustment for age, sex, duration of diabetes, A1C, BMI, hypertension, and LDL cholesterol. Even euthyroid patients with thyroid-stimulating hormone levels between 2.0 and <4.0 μIU/ml had a higher rate of STDR then those between 0.4 and <2.0 μIU/ml ($P = 0.008$).

CONCLUSIONS — Type 2 diabetic patients with SCH are associated with an increased risk of STDR.

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Diabetic retinopathy is one of the most common microvascular complications and the leading cause of blindness worldwide. Common risk factors for the development of microvascular complications include duration of diabetes, poor glycemic control, elevated blood pressure, and dyslipidemia (1,2).

Subclinical hypothyroidism (SCH) is defined as an asymptomatic state characterized by a normal serum thyroxin level and elevated serum concentration of thyrotropin (thyroid-stimulating hormone [TSH]). Patients with SCH sustain an obvious increase in cardiovascular event rates (3,4). Despite this, there is a distinct lack of relevant research into risk factors associated with microvascular complications in type 2 diabetes with SCH. In fact, only a single study conducted by Chen et al. (5) has attempted to elucidate these issues. Yet this study focused predominantly on the issue of diabetic nephropathy, as defined solely by elevated microalbuminuria, rather than retinopathy. However, in most diabetic patients with elevated microalbuminuria, other chronic kidney diseases should be considered in the absence of diabetic retinopathy (6). Our investigation examined the relationship between SCH and diabetic retinopathy in large Chinese type 2 diabetic patient samples.

RESEARCH DESIGN AND METHODS

— A total of 1,170 subjects comprising hospital-based patients with type 2 diabetes (aged 59.3 ± 14.0 years, with a mean duration of known diabetes for 8.8 ± 6.8 years) were investigated. Those with normal free triiodothyronine (FT3), free thyroxine (FT4), and an increased TSH (≥4 μIU/ml) level were diagnosed with SCH. We further divided euthyroid type 2 diabetic patients into two subgroups (TSH: 2.0 to <4.0 vs. 0.4 to <2.0 μIU/ml) and compared the two based on a more stringent "normal" reference interval of TSH suggested by the National Health and Nutrition Examination Survey (NHANES) III (7). All type 2 diabetic patients with SCH and 200 cases of euthyroid type 2 diabetic patients randomly selected from the 1,170 subjects were included in the further investigation. Digital retinal photographs (two eyes × two fields), taken using a TRC-NW7SF (Topcon, Tokyo, Japan) non-mydriatic camera at 45°, were examined independently by two qualified retinal photography graders following quality assurance protocols. The severity of diabetic retinopathy was graded based on the international clinical diabetic retinopathy severity scale (8). Eyes with more severe than moderate nonproliferative diabetic retinopathy were classified as sight-threatening diabetic retinopathy (STDR). Others were considered as having non–sight-threatening diabetic retinopathy (NSTDR). Data were analyzed by an unpaired Student *t* test, Mann-Whitney *U* test, Fisher exact test, χ^2 test, and multiple logistic regression.

RESULTS

— A total of 127 (10.9%) type 2 diabetic patients had SCH. No significant differences between the SCH and euthyroid groups in age, duration of known diabetes, BMI, systolic blood pressure, or biochemical parameters were found, except diastolic blood pressure, LDL cholesterol, and glomerular filtration rate (GFR). The trend to severe retinopathy in the SCH group was significantly higher than in the non-SCH group ($\chi^2 = 20.43$, $P = 0.000$) (Table 1).

After an adjustment for potential explanatory variables (age, duration of diabetes, A1C, BMI, blood pressure, and LDL

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Table 1—*Characteristics of type 2 diabetic patients with or without subclinical hypothyroidism*

	Euthyroidism	Subclinical hypothyroidism	*P*
n	200	127	—
Age (years)	58.3 ± 14.16	61.0 ± 13.7	0.110
Sex (M/F)	106/94	43/84	**0.001**†
Diabetes duration (years)	8.9 ± 6.9	8.3 ± 6.6	0.678
BMI (kg/m^2)	24.6 ± 3.4	24.8 ± 3.6	0.816
Systolic blood pressure (mmHg)	160.0 ± 20.1	168.7 ± 9.9	0.251
Diastolic blood pressure (mmHg)	82.1 ± 8.9	94.0 ± 3.5	**0.037**
Total cholesterol (mmol/l)	4.89 ± 1.24	5.18 ± 1.19	0.103
Triglycerides (mmol/l)	1.97 ± 1.92	1.90 ± 1.37	0.559
LDL cholesterol (mmol/l)	3.07 ± 0.95	3.31 ± 1.01	**0.031**
HDL cholesterol (mmol/l)	1.21 ± 0.33	1.23 ± 0.36	0.958
Blood urea nitrogen (mmol/l)	5.37 ± 2.52	5.20 ± 1.80	0.842
Creatinine (μmol/l)	74.5 ± 33.6	74.0 ± 25.3	0.586
Urinary albumin excretion rate (μg/min)	12.8 (1.18−4,631)	15.8 (1.32−1,875)	0.247*
Glomerular filtration rate	65.5 (24.3−113.8)	57.7 (24.8−106.3)	**0.000***
Alanine aminotransferase (IU/l)	16.0 ± 10.5	16.0 ± 9.0	0.638
Aspartate aminotransferase (IU/l)	17.0 ± 12.9	17.0 ± 11.0	0.322
Free triiodothyronine (pmol/l)	4.04 ± 2.46	3.84 ± 0.80	0.382
Free thyroid hormone (pmol/l)	17.0 ± 2.7	13.4 ± 2.4	**0.000**
TSH (μIU/l)	1.34 (0.16−3.77)	5.45 (4.12−28.3)	**0.000***
Diabetic retinopathy [*n* (%)]			
Proliferative diabetic retinopathy	16 (8.0)	21 (16.5)	**0.000**‡
Severe NPDR	12 (6.0)	22 (17.3)	
Mild and moderate NPDR	59 (29.5)	28 (22.0)	
Normal	100 (50.0)	44 (34.6)	
Unknown	13 (6.5)	12 (9.4)	

Data are means ± SD or median (range) unless otherwise indicated. MNPDR, mild and moderate NPDR; NPDR, nonproliferative diabetic retinopathy; SNPDR, severe NPDR. Unknown, withcataracts or could not check the ocular fundus. Student *t* test;*Mann-Whitney *U* test; †Fisher exact test; ‡Pearson χ^2 test, χ^2 = 20.43. Data in bold are statistically significant.

cholesterol), SCH was also associated with diabetic retinopathy [odds ratio (95% CI): 2.02 (1.18–3.46), $P = 0.011$] and STDR [4.15 (2.17–7.96), $P = 0.000$]. Additionally, type 2 diabetic patients with SCH had a significantly lower glomerular filtration rate.

In 200 euthyroid type 2 diabetic patients, 187 patients without cataracts were analyzed. Of the 187 patients, 15 of 125 patients (12.0%) with a TSH level between 0.4 and 2.0 mU/l had STDR, while 13 of 34 patients (38.2%) with a TSH level between 2.0 and <4.0 μIU/ml had STDR. A subgroup with a higher TSH level had a significantly higher rate of STDR (Fisher exact test, $P = 0.008$).

CONCLUSIONS — SCH is a common endocrine disorder and has been reported to range from 4 to 10% in large general population screening surveys (9) and has been found to be 4–17% in diabetic patients in previous studies (10).

SCH is an asymptomatic stage of hypothyroidism, but it is often complicated with endothelial dysfunction, including capillary and precapillary arterioles, manifested by thickening of the capillary basement membrane (11). Serum high-sensitive C-reactive protein levels in subjects with SCH were higher than control subjects (12). These changes lead to small vessel dysfunction (13), increasing the prevalence of retinopathy. The reference range for "normal" TSH has been the focus of considerable debate. Some clinicians have advocated reducing the upper limit of the normal reference interval for TSH to 2.5 or 3.0 mIU/l. Individuals in the 3.0–5.0 mIU/l TSH range are considered as possibly exhibiting the early signs of developing hypothyroidism, prompting continued monitoring (14). Our study supports this, since euthyroid patients with TSH levels between 2.0 and <4.0 μIU/ml demonstrated a higher rate of STDR than patients with levels between 0.4 and <2.0 μIU/ml.

Concerning limitations, this study is a cross-sectional study and cannot offer an explanation as to why type 2 diabetic patients with SCH had a high level of C-peptide and "better" glucose control, a finding which may warrant further investigation.

Routine screening for thyroid function in the general population and thyroxin replacement in patients with TSH within 4–10 μIU/ml is still controversial (15). Our findings suggest that type 2 diabetic patients with SCH demonstrated a higher prevalence of retinopathy than their non-SCH counterparts. A randomized controlled trial may provide evidence to support screening of thyroid function and the potential treatment of SCH in type 2 diabetic patients.

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