Endocrine Journal 2011, **58** (12), 1065-1070

ORIGINAL

Association between subclinical hypothyroidism and severe diabetic retinopathy in Korean patients with type 2 diabetes

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Abstract. The association between subclinical hypothyroidism (SCH) and microvascular complications of type 2 diabetes is unclear. We examined whether SCH is associated with diabetic retinopathy or nephropathy in Korean patients with type 2 diabetes. Data from 489 patients who visited the diabetes clinic at a university hospital between 2001 and 2007 were analyzed retrospectively. Participants were evaluated for glycemic control, thyroid function, and diabetic retinopathy and nephropathy. Diabetic retinopathy was classified into five grades. Diabetic nephropathy was assessed by the presence of albuminuria. Patients in the SCH group had a higher proportion of women, older age, longer duration of diabetes, higher systolic and diastolic blood pressure, and higher insulin resistance index compared with the euthyroid group. No significant difference in family history of diabetes or body mass index was found between groups. The prevalence of severe diabetic retinopathy (severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy) was significantly higher in the SCH group than the euthyroid group (32.8% *vs*. 19.6%, $P = 0.036$), whereas no between-group difference was found in the prevalence of diabetic nephropathy. After adjustment for potential confounding factors (HbA1c, BMI, duration of diabetes, diabetic nephropathy, and hypertension) by multivariate logistic regression analysis, SCH remained significantly associated with severe diabetic retinopathy (odds ratio 2.086 (95% CI, 1.010-4.307), $P = 0.047$). These results suggest that SCH was independently associated with severe diabetic retinopathy in patients with type 2 diabetes. Further prospective studies are required to confirm the association between SCH and diabetic retinopathy.

Key words: Subclinical hypothyroidism, Type 2 diabetes mellitus, Microvascular complications, Diabetic retinopathy

SUBCLINICAL HYPOTHYROIDISM (SCH) is an asymptomatic condition characterized by a normal serum thyroxin level and elevated serum concentrations of thyrotropin. The association between type 2 diabetes mellitus and SCH is well known, with the reported prevalence of SCH in diabetes varying between 2.0 and 17% [1, 2]. Although SCH is common in patients with type 2 diabetes, the clinical importance of the biochemical abnormalities is unclear. SCH has been reported to be associated with endothelial dysfunction independent from other well-known atherosclerotic risk factors [3]. An independent association between SCH and the risk of coronary heart disease has also been repeatedly observed [4-6]. Despite this, few studies have been conducted to examine the association between SCH and microvascular complications in type 2 diabetes. To our knowledge, two reported studies have investigated the association between SCH and microvascular complications in type 2 diabetes. Chen *et al*. [7] reported that patients with type 2 diabetes and SCH were at increased risk of nephropathy and cardiovascular events, but not retinopathy. In contrast, Yang *et al*. [8] reported an association between SCH and sight-threatening diabetic retinopathy in patients with type 2 diabetes. Apart from these two contradictory reports in Chinese patients, no study has investigated the association between SCH and diabetic microvascular complications in other populations. In the present study, we examined whether SCH was associated with diabetic retinopathy or nephropathy in Korean patients with type 2 diabetes.

Submitted Aug. 10, 2011; Accepted Sep. 1, 2011 as EJ11-0199
Released online in J-STAGE as advance publication Sep. 17, 2011
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Patients and Methods

Patients

A total of 637 Korean patients with type 2 diabetes who visited the diabetes clinic at Soonchunhyang University Bucheon Hospital (Bucheon, Gyeonggi-do, South Korea) between 2001 and 2007 were screened for thyroid function. Individuals with overt hypothyroidism, overt or subclinical hyperthyroidism, or who were taking thyroid hormones were excluded. Furthermore, patients with type 1 diabetes mellitus, renal insufficiency (serum Cr >1.3 mg/dL), alcoholism, chronic liver disease, chronic infection, pregnancy, malignancy, or acute illness were also excluded. After excluding 148 individuals, in total, 489 patients were included in the study. They were assessed for glycemic control, thyroid function, diabetic retinopathy, and nephropathy. Subclinical hypothyroidism (SCH) was defined as an elevated level of thyroid stimulating hormone (TSH; >4.0 mIU/L) in the presence of normal serum free thyroxine (FT4) level (0.7-2.0 ng/dL). The present study was approved by the Institutional Review Board of the Soonchunhyang University Bucheon Hospital.

Clinical examination and laboratory measurements

Information concerning the duration of diabetes, family history of diabetes, and previous history of hypertension was obtained from the patients' medical records. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Hypertension was defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking antihypertensive medications. Glycosylated hemoglobin (HbA1c) was measured using an ion-exchange HPLC (Bio-Rad, Hercules, CA, USA). Serum TSH (Cisbio Bioassays, Bagnols/Ceze, France) and fasting plasma insulin (Immunotech, Prague, Czech Republic) were measured by immunoradiometric assay, and FT4 was determined by radioimmunoassay (Cisbio Bioassays). The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated using the formula: HOMA-IR = fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5.

Assessment of diabetic retinopathy and nephropathy

Diabetic retinopathy was evaluated by experienced ophthalmologists while the patients' pupils were dilated. If needed, fluorescein angiography was performed. Diabetic retinopathy was classified according to the following grades [9]: (1) no diabetic retinal damage, (2) mild non-proliferative diabetic retinopathy (NPDR), (3) moderate NPDR, (4) severe NPDR, and (5) proliferative diabetic retinopathy (PDR). Retinopathy more severe than moderate NPDR (severe NPDR and PDR) was defined as severe diabetic retinopathy. Albuminuria was determined by radioimmunoassay (Immunotech) using spot urine or time-collected urine. Microalbuminuria was defined as an albumin excretion rate of 20–200 μg/min, an albumin/creatinine ratio in spot urine of 30–300 mg/g, or a 24-h urine protein of 30–300 mg/day. Albuminuria exceeding the range of microalbuminuria was defined as overt albuminuria.

Statistical analyses

Statistical analyses were conducted using SPSS for Windows® 14.0 software (SPSS Inc., Chicago, IL, USA). Results are expressed as the mean ± SD. Variables with a skewed distribution, such as blood concentration of glucose, triglycerides, and HbA1c, were log-transformed before analysis. Unpaired Student's *t*-tests were used to compare between-group differences. The chi-squared test was used to compare frequencies. Multivariate logistic regression analyses were performed to estimate the odds ratios (ORs) for severe diabetic retinopathy after adjusting for other clinical and biochemical variables. A *P*-value of <0.05 was deemed to indicate statistical significance.

Results

The clinical characteristics of the study participants are shown in Table 1. The SCH group had a higher proportion of women, older age, higher prevalence of hypertension, and longer duration of diabetes than the euthyroid group. Furthermore, the systolic and diastolic blood pressure and HOMA-IR values were higher in the SCH group than in the euthyroid group. No significant difference between groups was found in family history of diabetes or BMI. Moreover, no significant between-group difference was observed in glycemic control, lipid profiles, serum creatinine, or hs-CRP.

The prevalence of severe diabetic retinopathy was significantly higher in the SCH group compared to euthyroid group (32.8% *vs*. 19.6%, $P = 0.036$), whereas no difference was found in the prevalence of diabetic nephropathy (Table 2). In multiple logistic regression analyses, age- and gender-adjusted ORs for severe dia-

Table 1 Clinical characteristics of type 2 diabetic patients with or without subclinical hypothyroidism (SCH)

	Euthyroidism (n=428)	SCH (n=61)	*P*-value
Sex (M/F) (%)	208/220 (48.6/51.4)	15/46 (24.6/75.4)	<0.001
Age (years)	57.8±11.8	61.7±9.8	0.014
Duration of DM (years)	6.9±6.6	8.9±7.0	0.040
Family history of DM (%)	33.0	27.9	0.258
Hypertension (%)	36.5	54.2	0.007
BMI (kg/m^2)	24.8±3.9	24.1±3.2	0.208
HbA1c (%)	8.8±2.0	8.4±1.9	0.161
Fasting plasma glucose (mg/dL)	178±67	165±59	0.166
Postprandial plasma glucose (mg/dL)	258±95	251±88	0.621
Creatinine (mg/dL)	0.93±0.17	0.90±0.16	0.111
Systolic BP (mmHg)	131±19	142±21	<0.001
Diastolic BP(mmHg)	78±12	81±13	0.046
Total cholesterol (mg/dL)	198±45	206±38	0.192
LDL cholesterol (mg/dL)	116±41	130±42	0.145
HDL cholesterol (mg/dL)	44±10	45±9	0.361
Triglycerides (mg/dL)	195±134	186±109	0.627
hs-CRP (mg/dL)	0.67±1.74	0.40±1.00	0.403
TSH (mIU/L)	1.82±0.89	6.36±3.75	<0.001
Free T4 (ng/dL)	1.18±0.28	1.08±0.23	0.023
HOMA-IR	4.11±4.55	6.19±4.55	0.001

Data are shown as mean ± SD. *P*-values were determined by unpaired *t*-test or Pearson χ^2 test. SCH, subclinical hypothyroidism; DM, diabetes mellitus; BMI, body mass index; BP, blood pressure; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment index for insulin resistance.

Table 2 Prevalences of diabetic retinopathy and diabetic nephropathy in type 2 diabetic patients with or without subclinical hypothyroidism

	Euthyroidism (n=428)	SCH (n=61)	*P*-value
Diabetic nephropathy, N(%)			0.281
No albuminuria	293 (75.1)	47 (79.7)	
Microalbuminuria	72 (18.5)	8 (13.6)	
Overt albuminuria	25 (6.4)	4 (6.7)	
Diabetic retinopathy, N(%)			0.036
Normal	256 (59.8)	26 (42.6)	
Mild NPDR	58 (13.6)	7 (11.5)	
Moderate NPDR	30 (7.0)	8 (13.1)	
Severe NPDR	32 (7.5)	9 (14.8)	
PDR	52 (12.1)	11 (18.0)	

P-values were determined by Pearson χ^2 test. SCH, subclinical hypothyroidism; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

betic retinopathy in type 2 diabetic patients with SCH was 1.918 (95% CI, 1.054-3.490, $P = 0.033$) (Table 3). After further adjustment for potential confounding factors, such as HbA1c, BMI, duration of diabetes, diabetic nephropathy, and hypertension, SCH remained significantly associated with severe diabetic retinopathy (OR 2.086 (1.010-4.307), $P = 0.047$). There was no significant difference in TSH levels according to the different stages of diabetic retinopathy in the SCH group ($P = 0.815$ by analysis of variance test) (Table 4).

Discussion

In this hospital-based study of Korean type 2 diabetic patients, SCH was associated with severe diabetic retinopathy, but not with nephropathy, independent of

Table 3 Multivariate logistic regression analysis for severe diabetic retinopathy in type 2 diabetic patients

Independent variable	Odds ratio	95% CI	*P*-value
Model 1			
Age (yr)	0.990	0.971 – 1.010	0.318
Gender (female)	1.417	0.893 – 2.248	0.139
SCH (yes/no)	1.918	1.054 – 3.490	0.033
Model 2			
Age (yr)	0.995	0.974 – 1.015	0.604
Gender (female)	1.379	0.843 – 2.256	0.200
BMI (kg/m^2)	0.948	0.887 – 1.013	0.118
HbA1c (%)	1.158	1.031 – 1.301	0.013
SCH (yes/no)	2.235	1.187 – 4.209	0.013
Model 3			
Age (yr)	0.968	0.943 – 0.994	0.017
Gender (female)	1.100	0.620 – 1.954	0.744
BMI (kg/m^2)	0.922	0.852 – 0.998	0.045
HbA1c (%)	1.132	0.981 – 1.307	0.089
Duration of diabetes (yr)	1.107	1.062 – 1.154	< 0.001
Hypertension (yes/no)	2.331	1.302 – 4.172	0.004
Diabetic nephropathy (yes/no)	2.223	1.254 – 3.941	0.006
SCH (yes/no)	2.086	1.010 – 4.307	0.047

Severe diabetic retinopathy, severe nonproliferative diabetic retinopathy and proliferative diabetic retinopathy; SCH, subclinical hypothyroidism

other clinical and biochemical factors.

The association between SCH and the risk of microvascular complications in type 2 diabetes has not been studied thoroughly. Two previous studies, one from Taiwan [7] and one from China [8], investigated the association between SCH and microvascular complications in type 2 diabetes; however, the results were contradictory. Our results were consistent with those of Yang *et al*. [8], showing that SCH was associated with sight-threatening diabetic retinopathy, but differed from those of Chen *et al*. [7] who reported an association between SCH and an increased risk of nephropathy, but not with retinopathy. Reasons for this discrepancy are unclear at present, but they may be related to differences in study design, characteristics of the participants, and ethnicity. Our study had a higher proportion of men and younger patients with poorer glycemic control than did that of Chen *et al*., and we excluded patients with renal insufficiency. In addition, the patients in our study underwent a comprehensive assessment for diabetic retinopathy, including a dilated eye examination performed by ophthalmology specialists, and fluorescein angiography.

Several mechanisms may be involved in the association between SCH and diabetic vascular complications. Atherogenic disturbances in lipid metabolism have been observed in patients with SCH [10, 11], and a correlation between diabetic retinopathy and dyslipidemia has been reported [12, 13]. Furthermore, statin therapy has been reported to reduce the development or severity of diabetic retinopathy [14, 15]. Thus, dyslipidemia in SCH may be responsible for the association between SCH and diabetic retinopathy. In our study, total cholesterol and LDL cholesterol levels tended to be higher in the SCH group than in the euthyroid group, although the difference was not statistically significant. Another possible mechanisms that link SCH and vascular disease has been suggested by experimental data showing that thyroid hormones inhibit collagen-induced platelet aggregation [16, 17] and directly

Table 4 Serum thyroid stimulating hormone (TSH) levels according to different stages of diabetic retinopathy in type 2 diabetic patients with subclinical hypothyroidism

Retinopathy group	Number	TSH (mIU/L)
no retinopathy	26	7.04 ± 5.32
mild NPDR	7	5.51 ± 2.38
moderate NPDR	8	5.92 ± 1.43
severe NPDR	9	6.23 ± 2.55
PDR	11	5.75 ± 1.00

Data are shown as mean ± SD. $P = 0.815$ for difference among groups by analysis of variance (ANOVA) test. NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

relax smooth muscle [18] *in vitro*. Furthermore, hypothyroidism is accompanied by a hypercoagulable state [19] and increased blood viscosity [20]. Finally, although we could not find any supporting evidence, the possibility that an elevation of TSH, apart from the lack of thyroid hormones, would directly act on the development and/or progression of diabetic retinopathy can not be excluded.

Insulin resistance may be involved in the association between SCH and diabetic retinopathy. Our study revealed that HOMA-IR was higher in the SCH group than in the euthyroid group. This is consistent with previous studies showing fasting hyperinsulinemia or insulin resistance in patients with SCH [21, 22]. Several studies have found that the presence of proliferative diabetic retinopathy is associated with insulin resistance in type 1 and type 2 diabetes [23, 24]. Retinal vascular damage and secondary ischemia-induced neovascularization could be promoted by defective fibrinolysis [25] or impaired vasodilation [26] associated with insulin resistance.

Although we did not analyze the relationship between SCH and prevalence of macrovascular complications in the present study, it is well known that insulin resistance is closely involved in diabetic macroangiopathy. Furthermore, thyroid dysfunction may amplify cardiovascular disease risk in diabetic patients through interrelationships with dyslipidemia, insulin resistance, and vascular endothelial dysfunction [27]. SCH has been associated with endothelial dysfunction [3], atherosclerosis, and ischemic heart disease [4-6] in non-diabetic subjects. However, few studies have reported the association of SCH with cardiovascular disease in type 2 diabetic patients [7]. Additional studies are needed to confirm the association with macrovascular diseases.

Whether treatment of subclinical hypothyroidism in patients with type 2 diabetes affects clinical course of retinopathy remains unanswered. Thyroid hormone replacement therapy may be beneficial in delaying or preventing the development and/or progression of diabetic retinopathy in type 2 diabetic patients with SCH, but we could not draw a definite conclusion since our study is observational in nature. Prospective controlled clinical trial is required to establish treatment guidelines for SCH in patients with type 2 diabetes.

Our study has several limitations. First, this was a cross-sectional analysis and could not determine causal relationships. Prospective controlled studies are needed to confirm the association between SCH and diabetic retinopathy in type 2 diabetes. Second, our study population was a cohort of patients cared for at a single center. Thus, our results may not be generalizable to all Korean patients with type 2 diabetes. However, the majority of our subjects were typical type 2 diabetic patients commonly encountered in outpatient diabetes clinics. Third, thyroid function was evaluated at a single time point. It has been reported that some patients with SCH develop overt thyroid failure, while others may revert to euthyroid status during the follow-up period [28, 29]. Follow-up thyroid function tests are needed to confirm the association between the clinical course of SCH and diabetic retinopathy.

Despite these limitations, the present study provides evidence that SCH is associated with severe diabetic retinopathy in Korean patients with type 2 diabetes, even after controlling for potentially confounding clinical variables. Further larger prospective studies are required to confirm the association between SCH and diabetic retinopathy in patients with type 2 diabetes.

Conflicts of Interest

None of the authors had any conflicts of interest related to this study.

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