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Subclinical Hypothyroidism Is a Risk Factor for Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

Zahra Heidari[1]*, Reza Asadzadeh[2]

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Abstract

Diabetic retinopathy (DR) is one of the most common complications of diabetes. The known risk factors for microvascular complications are uncontrolled diabetes, duration of diabetes, dyslipidemia, and hypertension. In addition to these conventional risk factors, other risk factors, such as hypothyroidism have recently been suggested. Adult patients with type 2 diabetes mellitus (T2DM) were recruited. All patients were evaluated for retinopathy. Various clinical and biochemical parameters, including thyroid function tests, were assessed and compared between groups. In this study, 928 patients with (T2DM) were included. Of all patients, 376 (40.52%) had DR. In patients with retinopathy, 115 (30.58%) had proliferative and 261 (69.42%) had nonproliferative retinopathy. In patients with nonproliferative DR, 34.48%, 32.95%, and 32.57% had mild, moderate, and severe nonproliferative DR, respectively. Of all patients, 91 (9.8%) had subclinical hypothyroidism. There was a significant relationship between subclinical hypothyroidism (SCH) and DR in these patients. In patients with retinopathy, 14.4% and in patients without retinopathy, 6.7% had SCH ($p<0.001$). In univariate logistic regression analysis, the chance of developing DR in patients with SCH was 2.33 times higher than patients without subclinical hypothyroidism, each unit increase in the thyroid-stimulating hormone significantly increases the chance of developing DR by 13%. The present study showed that in the population of patients with (T2DM), SCH is associated with DR, regardless of the conventional risk factors.

Keywords: Diabetes Mellitus Type 2, Hypothyroidism, Diabetic Retinopathy

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Brief Communication

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes and the most common cause of blindness in the working-age population worldwide. It occurs in one-third of diabetic patients and is associated with an increased risk of other serious vascular complications, such as stroke and coronary artery disease. Thus, it is crucial to study and introduce the risk factors associated with the occurrence and progression of DR. The known risk factors for microvascular complica-

Corresponding author: *Dr Zahra Heidari, heidari.z@zaums.ac.ir*

[1] Department of Endocrinology and Metabolism, Zahedan University of Medical Sciences, Zahedan, Iran
[2] School of Biology, Damghan University, Damghan, Iran

↑What is "already known" in this topic:
The known risk factors for diabetic retinopathy (DR) are uncontrolled diabetes, duration of diabetes, dyslipidemia, and hypertension. In addition to these conventional risk factors, other risk factors, such as hypothyroidism, have recently been suggested. The association of subclinical hypothyroidism (SCH) with type 2 diabetes mellitus (T2DM) is well-established. Limited studies have examined the association between SCH and DR, and the reported results are contradictory.

→What this article adds:
The present study showed that in the population of type 2 diabetic patients, SCH is associated with DR, regardless of the conventional risk factors. The chance of developing DR in patients with SCH was 2.33 times higher than patients without subclinical hypothyroidism.

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tions are uncontrolled diabetes, duration of diabetes, dyslipidemia, and hypertension (1). In addition to these conventional risk factors, other risk factors, such as hypothyroidism, have recently been suggested. Subclinical hypothyroidism (SCH) is an asymptomatic condition, characterized by normal thyroid hormones and an increased level of circulating thyroid-stimulating hormone (TSH). In surveys on general populations, the prevalence of SCH has been recorded to be between 4% and 10%.

The association of SCH with type 2 diabetes mellitus (T2DM) is well established, and its prevalence in diabetic patients has been estimated at 2% to 17%. Although SCH is common in T2DM, the clinical significance of its biochemical disturbances is unclear (2). Previous research has indicated an independent association between SCH and the risk of coronary artery disease, although few studies have examined the association between SCH and microvascular complications in patients with T2DM. Limited studies have examined the association between SCH and DR, and the reported results are contradictory (3-5). Therefore, in the present study, we aimed to investigate the association between SCH and DR in a population of type 2 diabetic patients.

This study was performed on patients with T2DM who were referred to endocrinology clinics in Zahedan, southeastern Iran, between February 2018 and July 2020. Diagnosis of diabetes was based on the American Diabetes Association diagnostic criteria. Inclusion criteria were type 2 diabetic patients aged >30 years old. Patients were excluded if they had malignancy, acute or chronic illness or infection, psychiatric diseases, chronic liver disease, plasma creatinine >2 mg/dL, and eGFR <60 mL/min/1.73m^2. Patients with type 1 DM, overt hypothyroidism (TSH ≥10), overt or subclinical hyperthyroidism, or who taking levothyroxine or antithyroid drugs were excluded. Receiving drugs, such as amiodarone, glucocorticoids, and consumption of iodine-containing contrast in the last 6 months, were the other exclusion criteria. Pregnant or lactating women were also excluded from the study.

Only type 2 diabetes patients with euthyroid or subclinical hypothyroid were included in the study. After completing the questionnaire, including information concerning the age, sex, duration of diabetes, family history, and drug history, patients were evaluated in terms of height, weight, blood pressure measurement, and developing DR. After 12 hours of fasting, blood samples were taken from all participants between 8 and 9 AM. Blood glucose, lipid profile, thyroid function tests, and other biochemical tests were performed on blood samples.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Zahedan University Ethics Committee for Human Studies approved the protocol. All participants provided informed consent.

The association between independent variables and DR was assessed with univariate and multivariate logistic regression models.

In this study, 928 diabetic patients were included, of whom 65.3% were women. The mean age of patients was 54.3 years (SD, 11.1) and the mean duration of diabetes was 6.3 years. Of all patients, 376 (40.52%) had DR. The mean duration of diabetes in patients with DR was significantly longer than patients without retinopathy (6.51 vs 6.17; p= 0.046). Also, the mean amount of HbA1c was significantly higher for patients with DR (7.74 vs 7.67; p = 0.012). In patients with retinopathy, 115 (30.58%) had proliferative retinopathy and 261 (69.42%) had nonproliferative retinopathy. In patients with nonproliferative DR, 34.48%, 32.95%, and 32.57% had mild, moderate, and severe nonproliferative DR, respectively.

Of all patients, 91 (9.8%) had SCH. There was a significant relationship between SCH and DR. Therefore, in patients with retinopathy 14.4% and in patients without retinopathy 6.7% had SCH (p < 0.001). Although among different groups of patients with retinopathy, the prevalence of SCH in patients with severe nonproliferative retinopathy and in patients with proliferative retinopathy was higher than patients with mild and moderate nonproliferative retinopathy, no statistically significant difference was found.

In the univariate logistic regression analysis, the duration of diabetes with an odds ratio (OR) equal to 1.06 and HbA1c with OR of 1.28 were significant variables for DR. SCH had a significant association with DR, so that the chance of developing DR in patients with SCH was 2.33 times higher than patients without SCH (p < 0.001). Also, each unit increase in TSH significantly increases the chance of developing DR by 13% (Table 1).

According to the multivariate logistics regression model, the chance of developing DR showed a significant relationship with the history of taking statins (OR, 1.56) and the history of both oral hypoglycemic agents (OHA) and insulin compared with the history of using only OHA (OR, 1.54). Having SCH increases the chance of developing DR by 2.2 times after removing the confounding effect of other model variables. Also, in the multivariate model based on TSH, each unit increase in TSH increases the chance of developing DR by 1.12 times (Table 2).

The results of the present study are consistent with the findings of studies conducted by Yang et al (6) and Kim et al (7), which showed that SCH is associated with severe DR. On the other hand, our findings contradict the results of a study by Chen et al (8), which showed no significant association between SCH and retinopathy. Although the exact cause of the discrepancy between the results is not clear, differences in the study design, characteristics of the study populations, and genetic and racial differences may be influential. It should be noted that our study differs from the study by Chen et al, as we included larger sample size, a different racial group, and younger patients.

SCH is a common endocrine disease with a prevalence of 4% to 10% in large population-based studies and a prevalence of 4% to 17% in diabetic patients (9). The association of SCH and DR with several mechanisms can be explained. Although SCH is an asymptomatic stage of hypothyroidism, it is often associated with endothelial dysfunctions, affecting the capillary endothelium and precapillary arterioles, and manifests as an increase in the

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Table 1. Univariate Logistic Regression Analyses of Diabetic Retinopathy

Variable	Wald Statistics	OR (95% CI)	P Value
Age	3.91	1.0 (0.992 to 1.01)	0.561
Sex, female	0.237	1.07 (0.813 to 1.41)	0.626
Diabetes duration	3.91	1.06 (1.0 to 1.11)	0.048*
Positive family history of DM	0.126	0.953 (0.733 to 1.24)	0.723
Use of antihypertensive drug	0.231	1.07 (0.819 to 1.39)	0.631
Use of statin	2.28	1.34 (0.918 to 1.94)	0.131
History of OHA use only	3.16	0.772 (0.581 to 1.03)	0.075
History of insulin use only	2.40	1.35 (0.924 to 1.97)	0.122
History of OHA and insulin	0.588	1.15 (0.806 to 1.64)	0.443
BMI (kg/m2)	0.166	1.01 (0.965 to 1.06)	0.683
Systolic blood pressure	0.556	1.01 (0.992 to 1.02)	0.456
Diastolic blood pressure	0.483	0.995 (0.980 to 1.01)	0.487
Fasting plasma glucose	0.155	1.0 (0.995 to 1.01)	0.693
HbA1c	6.16	1.28 (1.05 to 1.56)	0.013*
Total cholesterol	1.10	0.998 (0.995 to 1.0)	0.293
Triglycerides	0.542	1.0 (0.999 to 1.0)	0.462
LDL cholesterol	3.32	0.997 (0.993 to 1.0)	0.068
HDL cholesterol	0.001	1.0 (0.985 to 1.02)	0.978
VLDL	0.485	1.0 (0.993 to 1.01)	0.486
Blood urea nitrogen	0.173	0.992 (0.956 to 1.03)	0.677
Creatinine	0.894	0.705 (0.341 to 1.46)	0.344
ALT	2.21	1.01 (0.996 to 1.03)	0.138
AST	1.65	1.01 (0.995 to 1.03)	0.199
Alk.ph	0.088	1.0 (0.995 to 1.01)	0.766
FT3	0.372	0.937 (0.759 to 1.16)	0.542
FT4	0.059	0.936 (0.548 to 1.60)	0.808
TSH	14.98	1.13 (1.06 to 1.21)	<0.001*
SCH	14.20	2.33 (1.50 to 3.63)	<0.001*

*. Statistically significant of odds ratio in p-value<0.05
OR: Odds ratio; CI: Confidence interval
ALT: Alanine transaminase; AlkPH: Alkaline phosphatase; AST: Aspartate transaminase; BMI: Body mass index; BP: blood pressure; DM: Diabetes mellitus; FT3: Free triiodothyronine; FT4: free thyroxine; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TSH: Thyroid-stimulating hormone; OHA: Oral hypoglycemic agents; SCH: Subclinical hypothyroidism; VLDL: Very-low-density lipoprotein.

Table 2. Multivariate Logistic Regression Analyses of Diabetic Retinopathy

	Wald Statistics	OR (95% CI)	P Value
Model 1: based-on SCH			
Diabetes duration	0.140	0.987 (0.922 to 1.06)	0.709
Use of statin	4.45	1.56 (1.03 to 2.35)	0.035
History of drug use for DM			
Only use of insulin vs only OHA	0.234	1.11 (0.736 to 1.66)	0.629
Only use of OHA vs both*	4.35	1.54 (1.03 to 2.30)	0.037
HbA1c	0.178	1.05 (0.832 to 1.33)	0.673
LDL cholesterol	2.26	0.977 (0.993 to 1.0)	0.133
ALT	0.698	1.01 (0.991 to 1.02)	0.404
SCH	5.44	2.17 (1.13 to 4.14)	0.020
Model 2: based-on TSH			
Diabetes duration	0.038	0.994 (0.933 to 1.06)	0.846
Use of statin	4.44	1.56 (1.03 to 2.35)	0.035
History of drug use for DM			
Only use of insulin vs only OHA	0.394	1.14 (0.761 to 1.70)	0.530
Only use of OHA vs both*	4.79	1.57 (1.05 to 2.34)	0.029
HbA1c	0.391	1.07 (0.860 to 1.34)	0.532
LDL cholesterol	2.59	0.997 (0.993 to 1.0)	0.108
ALT	0.703	1.01 (0.991 to 1.02)	0.402
TSH	7.23	1.12 (1.03 to 1.21)	0.007

*. History of both insulin and OHA use.
OHA: Oral Hypoglycemic Agents.

thickness of the basement membrane of the capillaries. These changes lead to the dysfunction of small vessels, which may be one of the reasons for the increased prevalence of retinopathy in these patients (2).

Previous studies have shown that C reactive protein levels in patients with SCH are clearly higher than patients without SCH. In this regard, a previous study reported a significant association between the CRP level and DR. It is well established that DR is a chronic inflammatory disease, associated with inflammatory damage to vascular endothelial cells. Also, CRP is one of the most sensitive and primary proteins in the acute-phase inflammation reaction (10).

The serum level of homocysteine in patients with SCH is much higher than in non-SCH patients. Homocysteine is an amino acid that has been linked to vascular damage in previous studies. Previous studies showed that the serum homocysteine level is a risk factor for DR. This may be due to the fact that homocysteine can increase lipid peroxidation, which leads to an increase in low-density lipopro-

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tein oxidation and accelerates the progression of vascular disease. Previous researchers have shown that mRNA expression of vascular endothelial growth factor (VEGF) is increased significantly by increasing the homocysteine concentration, and the increased level of VEGF is significantly associated with the development of DR (11).

The association between DR and dyslipidemia has been reported in the literature. Moreover, atherogenic abnormalities in lipid metabolism have been observed in patients with SCH. In other words, another reason for the association between DR and SCH is dyslipidemia in these patients. Some studies have shown that treatment with statins could prevent or reduce the severity of DR (12).

Several studies have shown that insulin resistance, which is associated with increased fasting insulin levels, is related to SCH, On the other hand, insulin resistance is associated with the presence of DR in patients with T2DM. The main mechanism of this association is a defect in fibrinolysis and a decrease in vasodilation, along with insulin resistance, leading to the destruction of retinal blood vessels and secondary vascularization (13).

Oxidative stress is another essential mechanism involved in this association. Paraoxonase 1 activity and superoxide dismutase level in the plasma of patients with SCH are significantly lower than the controls; therefore, the antioxidant capacity is clearly reduced in SCH patients. Some studies have shown that oxidative stress is an important risk factor for the development or progression of DR (14).

Another mechanism involved in the association between vascular disease and SCH is the inhibition of collagen-induced platelet aggregation by thyroid hormones and direct relaxation of smooth muscles in the vascular wall by them. Although the level of thyroid hormones might seem normal in SCH patients, there could be a significant reduction relative to the previous set point in these patients. Also, hypothyroidism can be associated with a hypercoagulable state and increased blood viscosity; however, further investigation is required to determine whether these abnormalities are similar in SCH patients (15).

Finally, the elevated level of TSH in SCH, regardless of thyroid hormones, may be directly involved in the development or progression of DR, although there is no documented evidence. The present study has several limitations. First, it was a cross-sectional study that could not indicate the cause-and-effect relationship between SCH and retinopathy; therefore, prospective studies are required to confirm the correlation between these 2 conditions. Second, all of our diabetic patients were selected from a single referral center. Although most patients were typical type 2 diabetic patients in the community, the population could affect the external validity of the study. On the other hand, this study had an acceptable sample size. Also, thyroid function tests were repeated for patients with SCH within 6- to 8-week intervals, and they were included in the study as SCH patients if the patterns of thyroid tests were stable.

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Ethics Approval and Consent to Participate

We conducted study procedures after obtaining the ethical approval of the research committee (either organizational or national). In addition, we respected the principles of the 1964 Helsinki declaration and its amendments. The ethics committee of Zahedan University confirmed the study protocol. Informed consent was obtained from all participants.

Conflict of Interests

The authors declare that they have no competing interests.

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