# The Association between Subclinical Hypothyroidism and Diabetic Retinopathy in the Patient with Type 2 Diabetic

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## Abstract

The present study aimed to determine the relationship between subclinical hypothyroidism and diabetic retinopathy in patients with type 2 diabetes mellitus. In this cross-sectional analytical study, 150 patients with type 2 diabetes mellitus were assessed. The eye fundus examination was performed using fundoscopy to confirm or rule out retinopathy. Thyroid hormones were also measured by special kits to diagnose subclinical hypothyroidism. The criteria for diagnosis of this disorder include the high serum thyrotropin concentration (≥ 4mIU/L) plus normal serum free thyroxin levels. Statistical analyses were done using IBM-SPSS. In the study, 34.66% suffered retinopathy. A total of 24.0% suffered subclinical hypothyroidism with higher prevalence rate in those with retinopathy as compared with the group without retinopathy (p = 0.001). Those with diabetic retinopathy also experienced longer duration of diabetes than those without this event. (p = 0.006). Analysis show a significant role for type 2 diabetes mellitus (OR = 1.121, P = 0.003), and high TSH level (OR = 1.342, P = 0.006) to predict diabetic retinopathy.This study showed an association between hypothyroidism, diabetes and increased TSH with retinopathy. Retinopathy is significantly predicable with the presence of subclinical hypothyroidism and longer duration of diabetes.

***Keywords:*** *Diabetes mellitus, Subclinical hypothyroidism, Retinopathy*

## Introduction

Type 2 diabetes mellitus is a major group of disorders characterized by varying degrees of insulin resistance, reduced insulin secretion and increased glucose production that affects around 285 million people worldwide in 2010, with a rapidly increasing prevalence around the world [(1)] . The prevalence of this phenomenon is 0.2% in people under age 20, 11.3% in people over the age of 20 and 26.9% in people over 65 years of age. Meanwhile, due to an increase in the prevalence of obesity and a decrease in physical activity, the increase in the prevalence of type 2 diabetes mellitus has been higher than imagined [(2)]. In diabetic patients, there are many acute and chronic complications that can be attributed to cardiovascular, renal, neurological, infectious and ocular complications [(1, 3)] . Diabetic retinopathy is an ophthalmologic complication of diabetes mellitus and one of the causes of blindness in people with this disease [(1, 4)]. Prolonged diabetes, poorly controlled blood glucose, advanced age, male gender, increased systolic blood pressure, consuming antihypertensive medications can increase the likelihood of diabetic retinopathy [(5)]. Given that the prevalence of diabetes is increasing, the progression of diabetic retinopathy is also rising as one of the microvascular complications of diabetes mellitus [(6)]. The prevalence of retinopathy, non-proliferative retinopathy and proliferative retinopathy was 3.1%, 1.1% and 0.1% in the general population and 23%, 19.1% and 8.2% in the diabetic population, respectively. Since the most effective treatment for diabetic retinopathy is to prevent it, the importance of identifying risk factors and the

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causes of increased prevalence of diabetic retinopathy is clarified [2, 4]. The thyroid plays an important role in the body's metabolism [7] and recently suggested that the prevalence of people with thyroid disorders, especially subclinical hypothyroidism, was significantly higher in people with type 2 diabetes mellitus. Subclinical hypothyroidism is an asymptomatic stage of hypothyroidism characterized by elevated serum thyrotropin levels and serum free thyroxine levels [8]. Patients with subclinical hypothyroidism have an endothelial dysfunction, which may lead to dysfunction of the small veins as the main fundament of retinopathy [8, 9]. Some Studies demonstrated association between high thyroid stimulating hormone (TSH) levels and an increased risk of diabetic [10, 11] and some studies do not show this relationship [12] For this reason, in many studies, it is recommended that people with thyroid disorders, especially subclinical hypothyroidism, should be screened for retinopathy so that the condition can be given to health authorities in a controlled manner. Therefore, due to the high prevalence of diabetes and hypothyroidism and various complications due to the lack of control of diabetes, especially retinopathy, and the possible association of these two diseases with diabetic retinopathy, the present study aimed to determine the relationship between subclinical hypothyroidism and diabetic retinopathy in patients with type 2 diabetes mellitus.

## Materials and Methods

**Study design:** In this cross-sectional analytical study, 150 patients with type 2 diabetes mellitus who referred to the internal clinic of Kowsar Hospital of Semnan between 2013 and 2014, with the preservation of inclusion and exclusion criteria were assessed. The sampling method was convenience sampling. Furthermore, data were collected through a questionnaire and Para clinical results.

**Inclusionand exclusion criteria:** The inclusion criteria were having type II diabetes mellitus, disease duration ranged 2 to 5 years, serum hemoglobin A1C 6.5% or higher, lack of clinical manifestations of thyroid disorders including fatigue, malaise, skin dryness, puffiness of face and hands, lack of laboratory findings related to thyroid disorders including raised TSH level along with reduced free T4, and conscious consent to participate in the study. In this regard, those with the history of cancer, liver or kidney disorders, chronic infections, using the drugs affecting thyroid functions (such as glucocorticoids, oral contraceptives, or NSAIDS) were all excluded from the study.

**Study protocol and Biologic samples:** After taking the medical records including demographics, medical history and medications, a clinical examination was performed to determine height, weight and blood pressure. Also, thyroid stimulating hormone (TSH), free thyroxine (free T4), hemoglobin A1C (HBA1C) and fasting blood glucose (FBS) were measured at the hospital laboratory using the special kits. TSH and T4 levels were measured by radioimmunoassay technique. HBA1C was measured by high-performance liquid chromatography (HPLC). FBS Fasting blood glucose was also measured by a glucose oxidase method. The eye fundus examination was performed using fundoscopy. The information was included in the data collection forms, which was previously prepared by the researcher for this purpose. This work continued until the sample volume was completed.

Data collection: Venous blood samples were collected in test tubes containing clot activator, immediately stored on ice, and—one hour after collection—centrifuged at 4000 rpm for 10 minutes. Plasma were separated and stored at −80°C through the hour to be analyzed. Those with normal free thyroxine (FT4) and an increased TSH (≥4 μIU/ml) level were diagnosed with SCH. 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. data of patients and laboratory results were recorded in a pre-designed information form and finally entered for statistical analysis.

Statistical analysis: Descriptive analysis was used to describe the data, including mean ± standard deviation (SD) for quantitative variables and frequency for categorical variables. Chi square test, independent t test were used for comparison of variables. The correlation between quantitative variables was tested by the Pearson's correlation test. For the statistical analysis, the

statistical software IBM SPSS Statistics for Windows version 25.0 was used. P values <0.05 were considered statistically significant.

## Findings

In this study, 150 patients with type 2 diabetes mellitus were analyzed. The mean age of patients was 57.94 ± 9.68 years including 93 men (62.0%) and 57 females (38.0%). Of the participants in the study, 52 (34.66%) suffered retinopathy. None of the patients has overt or clinical hypothyroidism. Comparing baseline characteristics between the patients with and without retinopathy showed no difference in patients' age (p = 0.232), gender (p = 0.329), body mass index (p = 0.431) (Table 1).

**Table 1: Comparing baseline characteristics between the groups with and without retinopathy**

| Item | Group with retinopathy | Group without retinopathy | P value |
|---|---|---|---|
| Age subgroups | | | 0.232 |
| < 50 years | 5 (9.6) | 25 (25.5) | |
| 50-59 years | 19 (36.5) | 41 (41.8) | |
| 60-69 years | 16 (23.1) | 21 (21.5) | |
| ≥ 70 years | 12 (23.1) | 11 (11.2) | |
| Female gender | 34 (65.4) | 59 (60.2) | 0.329 |
| Disease duration | 13.73 ± 1.06 | 9.03 ± 0.51 | 0.006 |
| 5-10 years | 25 (48.1) | 70 (71.4) | |
| 11-20 years | 18 (34.6) | 23 (23.5) | |
| 21-30 years | 8 (15.4) | 5 (5.1) | |
| >30 years | 1 (1.9) | 0 (0.0) | |
| Body mass index | 26.21 ± 0.58 | 25.63 ± 0.46 | 0.431 |
| < 25 kg/m2 | 22 (42.3) | 44 (44.9) | |
| 25-29.9 kg/m2 | 19 (36.5) | 33 (33.7) | |
| ≥ 30 kg/m2 | 11 (21.2) | 21 (21.4) | |

Results showed that subclinical hypothyroidism is associated with retinopathy and this relationship is statistically significant. No significant correlation systolic blood pressure (p = 0.365), diastolic blood pressure (p = 0.685), the level of fasting blood sugar (p = 0.401), and HBA1C level (p = 0.466), while those with diabetic retinopathy experienced longer duration of diabetes than those without this event. (13.73 ± 1.06 years versus 9.03 ± 0.51 years, p = 0.006). The mean level of TSH in the patients with and without retinopathy was 4.68 ± 0.96 and 2.13 ±0.18 with significant difference (p = 0.006) (Table 2).

**Table 2 Comparing Biochemical characteristics**

| Item | Group with retinopathy | Group without retinopathy | P value |
|---|---|---|---|
| Mean systolic blood pressure, mmHg | 127.00 ± 2.00 | 123.44 ± 1.31 | 0.365 |
| Mean diastolic blood pressure, mmHg | 78.60 ± 1.15 | 78.79 ± 0.85 | 0.658 |
| Fasting blood sugar, mg/dl | 159.52 ± 13.06 | 148.81 ± 5.62 | 0.401 |
| < 100 mg/dl | 11 (21.2) | 14 (14.3) | |
| 100-126 mg/dl | 11 (21.2) | 29 (29.6) | |
| >126 mg/dl | 30 (57.7) | 55 (56.1) | |
| Mean hemoglobin A1C | 7.89 ± 0.20 | 7.77 ± 0.16 | 0.466 |
| Mean TSH level | 4.68 ± 0.96 | 2.13 ± 0.18 | 0.006 |
| Prevalence of hypothyroidism | 36 (24.0) | 22 (42.3) | 0.001 |

A total of 36 patients (24.0%) suffered subclinical hypothyroidism with higher prevalence rate in those with retinopathy as compared with the group without retinopathy (42.3% versus 14.3%). However, there was no difference in the level of T4 between the patients with and without diabetic retinopathy (1.10 ± 0.04 ng/dL versus 1.20 ± 0.02 ng/dL, p = 0.222). In order to investigate the relationship between the mentioned variables on retinopathy, logistic regression analysis showed that type 2 diabetes mellitus was significantly associated with retinopathy (OR = 1.121, 95%CI: 1.041 – 1.208, P = 0.003), and high TSH level (OR = 1.342, 95%CI: 1.086 – 1.657, P = 0.006) to predict diabetic retinopathy (Table 3).

**Table 2: Multivariable logistic regression model to predict diabetic retinopathy**

| Item | Beta | Wald | P value | Lower limit | Upper limit |
|---|---|---|---|---|---|
| Age | 0.014 | 0.378 | 0.540 | 0.969 | 1.063 |
| Gender | -0.048 | 0.013 | 0.909 | 0.418 | 2.174 |
| Type 2 diabetes mellitus | 0.115 | 9.119 | 0.003 | 1.041 | 1.208 |
| Systolic blood pressure | 0.028 | 2.827 | 0.093 | 0.995 | 1.063 |
| Diastolic blood pressure | -0.024 | 0.850 | 0.357 | 0.927 | 1.028 |
| Body mass index | 0.063 | 1.883 | 0.170 | 0.973 | 1.165 |
| Fasting blood sugar | 0.001 | 0.027 | 0.870 | 0.994 | 1.007 |
| Hemoglobin A1C | -0.025 | 0.028 | 0.867 | 0.724 | 1.312 |
| Free T4 | -0.530 | 0.484 | 0.486 | 0.133 | 2.616 |
| TSH | 0.294 | 7.454 | 0.006 | 1.086 | 1.687 |

## Discussion

In our study, it was found that subclinical hypothyroidism is directly and significantly associated with retinopathy. Also, retinopathy was directly and significantly associated with Type 2 diabetes mellitus and TSH levels. Coherent research has shown Patients with subclinical hypothyroidism have an endothelial dysfunction, which may lead to inappropriate operation of small veins increasing the likelihood of retinopathy [8, 9]. The association between thyroid hormone levels and retinopathy has been observed in other studies [10, 11, 13]. For this reason, in many studies, it is recommended that people with thyroid disorders, especially subclinical hypothyroidism should be screened for retinopathy. In study on 1581 subjects with normal thyroid function, the results showed that TSH levels had a positive correlation with insulin resistance and, as a result, with diabetic retinopathy [14] .In another study conducted on the Beijing Tongren Hospital of China on 1,117 patients with type 2 diabetes mellitus, it was found that the prevalence of diabetic retinopathy in people with subclinical hypothyroidism was higher than those with normal thyroid [9]. Also, although the level of fasting blood glucose and hypertension are known to be two factors affecting diabetes [15-17], Yuedong Hu (2015) noted that these two factors had no meaningful relationship with diabetic retinopathy [18]. Moreover, in a study of 11140 patients with type 2 diabetes mellitus, the results showed that control of blood pressure below the normal level, even for 5 years, had no significant effect on the prevalence of diabetic retinopathy [19] , which was similar to our findings. In a study conducted by Javadi et al. (2009) in Saudi Arabia, more than 50% of people with diabetic retinopathy were older than 60 years of age [20], which was also similar to our study results. Similarly, in a study by Khalid Al-Rubeaan et al. (2015), unlike our study, the prevalence of diabetic retinopathy in males was more than females [21]. The reason for this was the lower number of males in our study than the similar studies, which reduced the likelihood of diabetic retinopathy in men. additionally, obesity is a problem because of the direct relationship with diabetes [22, 23] . In this regard, Studies noted that the BMI of diabetic individuals had a meaningful relationship with diabetic retinopathy [21, 24, 25], but in our study, there was no significant relationship between BMI and risk for retinopathy.

One of the most important limitations of this study was its cross-sectional nature that limited the outcome analysis. Another limitation in this study was the relatively small number of statistical samples that should be cautious about generalizing its outcomes to other individuals and populations. Also, in this study, the definition and division of obesity has been done based on the BMI of individuals; while this index does not differentiate between muscle distribution and fat distribution. Even the distribution of fat in different parts of the body could have changed the risk of developing diabetes in different individuals, as the results of various studies indicate that the distribution of fat levels in the upper and lower abdomen, the risk Metabolic diseases, especially diabetes, are increased more than those who have a fat mass in the lower parts of the body [26-29].

One of the other limitations of this study was the lack of examination of a number of diabetes-related factors mentioned in other studies, including smoking, as well as exercise and physical activity, which, of course, due to the limited means of measuring this study. Also, the treatment of diabetics (insulin or oral medication) was another issue that could not be verified due to the limitations of this study.

## Conclusion

Subclinical hypothyroidism is associated with diabetic retinopathy in type 2 diabetic patients. There is a positive correlation between level of TSH and Intensity of diabetic retinopathy in type 2 diabetics with subclinical hypothyroidism. Also, subclinical hypothyroidism was one factor that significantly increased the risk of diabetic retinopathy. Therefore, considering the high prevalence of diabetic retinopathy and its relation to the subclinical hypothyroidism, planning for the education of patients at risk for diabetes or diabetic patients regarding long-term complications of diabetes, especially retinopathy is essential.

**Ethical Clearance:** Obtained from institutional ethical committee

**Source of Funding:** Self

**Conflict of Interest**: Nil

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