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Original article

Association Between Subclinical Hypothyroidism and HbA1c Levels in Non-Diabetic Patients: A Case-Control Study

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Abstract

Diabetes mellitus (DM) is a chronic endocrine disorder. Previous studies have indicated a potential connection between subclinical hypothyroidism (SH), insulin resistance, and altered blood sugar levels. This study aimed to compare HbA1c levels between nondiabetic individuals with SH and healthy controls with normal thyroid function. A case-control study was conducted with 200 participants, including those with SH and healthy controls (HCs). Serum levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), HbA1c, and fasting plasma glucose were measured. Statistical analysis was performed to assess the differences between the groups and the correlation between HbA1c and TSH, and T3 and T4. Significant differences were observed in the mean HbA1c (P=0.0002) and TSH (p = 0.0001) levels between the control and SH groups. However, no significant differences were found in the mean age of fasting plasma glucose FBG, T3, and T4 levels between the groups. HbA1c levels were positively correlated with serum TSH levels (r=0.684, P<0.00001). In conclusion, our study identified a significant positive correlation between HbA1c and TSH levels in individuals with subclinical hypothyroidism. Therefore, assessing HbA1c levels in patients with hypothyroidism may be crucial for diagnosing diabetes or prediabetic states.

***Keywords.** Subclinical Hypothyroidism, TSH, HbA1c, Non-diabetic.*

Introduction

The World Health Organization (WHO) and the American Diabetes Association (ADA) have recently endorsed the use of HbA1c for both screening and diagnosing diabetes[1, 2]. Hemoglobin A1c (HbA1c) is the main form of glycated hemoglobin [3, 4]. According to ADA guidelines, an HbA1c level > 6.5% indicates diabetes, whereas levels between 5.7% and 6.4% suggests a prediabetic state [5,6].

However, previous research has shown that HbA1c levels can vary under certain conditions, such as hemoglobinopathies, chronic kidney disease, and pregnancy, even in the absence of diabetes [7, 8]. Since HbA1c is influenced not only by blood glucose levels but also by the lifespan of erythrocytes, any condition that affects erythrocyte turnover or survival can result in inaccurate low or falsely elevated HbA1c readings [9].

Hypothyroidism is another condition that can cause significant metabolic disturbances leading to various clinical symptoms [10, 11]. Thyroid dysfunction, including hypothyroidism, is more prevalent in individuals with type 2 diabetes mellitus (T2DM) than in the general population. Studies by Kim MK and colleagues have demonstrated that patients with hypothyroidism can have spuriously elevated HbA1c levels even in the absence of diabetes [12, 13]. This suggests that hypothyroidism may interfere with HbA1c measurements, potentially leading to the misinterpretation of glycemic control [14, 15]. This spurious elevation is thought to be due to the prolonged lifespan of erythrocytes in hypothyroid patients, allowing more time for glucose to bind to hemoglobin, thereby increasing HbA1c levels. This highlights the importance of considering thyroid function when interpreting HbA1c results [15, 16].

Subclinical hypothyroidism (SH), characterized by elevated serum TSH levels with normal T4 and T3 levels and no apparent clinical symptoms, is another condition of interest [17, 18]. In this study, we aimed to explore the relationship between subclinical hypothyroidism and HbA1c levels in non-diabetic Libyan adults residing in Zeletin city.

Methods

Study design

Blood (This analytical cross-sectional study was conducted over five months, from January to May 2024, in clinics located in Zeletin city, Libya, following approval from the Institutional Ethics Committee. The study included 200 participants of both sexes, aged 18 years and older. Of these, 128 individuals were placed in the control group, while 72 participants who had been diagnosed with subclinical hypothyroidism but had not yet received treatment were included as cases. Individuals with a history of anemia, diabetes, thyroid disorders, liver disease, or renal disease were excluded from the study.

Data collection

Blood samples were collected from all subjects, out of which, 3 ml was transferred to clot activator tubes (red top tubes), Serum T3, T4 and TSH were estimated using the Ichroma
2 ml of blood was collected in EDTA tubes containing an anticoagulant for analysis of Fasting Blood Glucose (FBG) and HbA1c. Auto analyzer A 15 was used to measure Fasting Blood Sugar (FBS) levels. HbA1c levels were measured using an I-chroma analyzer, which is based on a fluorescence immunoassay (FIA) and is specifically designed to determine HbA1c in human whole blood. Glycated hemoglobin, represented by HbA1c, is expressed as a percentage of total hemoglobin in the blood.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 22.0; IBM SPSS, Armonk, NY, USA). Data were summarized as means and standard deviations of HbA1c, FBG, TSH, T3, T4, and Age and were compared between the two groups and analyzed using Student's independent "t" test. The association between T3, T4, TSH, and HbA1c levels was examined using linear regression analysis. To compare the differences in HbA1c levels between males and females, a two-sample t-test was used. Statistical significance was set at $P < 0.05$.

Results

This study included 200 participants, with 72 and 128 subjects in the case and control groups, respectively. All participants were aged between 18 and 83 years. Table 1 outlines the distribution of male and female participants across different age groups, divided into "Control" and "Case" categories, and then combined for the "Total."

The mean age of participants in the case group was 44.9±15.2years, while the mean age in the control group was 46.3±15.9 years. The two groups were comparable in age, with a p-value of 0.65, indicating no significant difference between them. The case groups had 40 males and 34 females, and in the control group, 54 males and 72 females (p-value of 0.3). The table2. presents the results of a linear regression analysis, where HbA1c is the dependent variable and TSH, T3, and T4 are the independent variables. TSH was the only variable that was significantly associated with HbA1c levels. Specifically, TSH had an unstandardized coefficient (B) of 1.801 ($p = .002$), indicating that for every one-unit increase in TSH, HbA1c increased by 1.801 units, holding other variables constant. The standardized coefficient (beta) for TSH was 0.452, reflecting its strong influence on HbA1c levels, while T3 and T4 did not show significant associations with HbA1c. The unstandardized coefficients for T3 was 0.007 ($p = .274$), and for T4, it was -0.083 ($p = .432$), respectively.

Table 1. **Demographic data of the case and the control groups.**

Age Years	Control		Case		Total	
	Male	Female	Male	Female	Male	Female
18-29	24	25	6	5	30	30
30-39	13	14	6	4	19	18
40-49	5	15	13	10	18	25
50-59	8	9	6	6	14	15
Above 60	4	9	9	9	13	18
Total	54	72	40	34	94	106

Table 2. The correlation between the levels HbA1c and all the subjects

Variable	β	SE	*t*-value	*P*-value
Constant	3.745	1.315	2.848	.006
T3	.007	.006	1.107	.274
T4	-.083-	.104	-.793-	.432
TSH	1.801	.557	3.235	.002

The results of the comparison of the case and control groups are presented in Table 3. There were no statistically significant differences in FBG, T3, or T4 levels between the groups. However, the mean HbA1c level was significantly higher in the case group (7.5±2.6%) than in the matched control group 6.4±2.0%). This difference was statistically significant (p = 0.0002), indicating that the elevation in HbA1c levels in the case group was not due to random variation but was likely a meaningful difference between the groups. The mean serum TSH level was different between the groups, with the case group having a mean TSH level of 5.1 ± 1.62 mU/L, compared to 1.7 ± 0.79 mU/L in the control group. This difference was statistically significant (p = 0.0001), indicating that the serum TSH levels were markedly higher in the case group than in the control group.

Table 3. Comparison of the various parameters in the case and the control groups. (The independent t-tests). *p < 0.05 = Statistically Significant

Parameters	Control	Case	*P*-value
Age (Year)	44.9±15.2	46.3±15.9	0.56
HbA1c (%)	6.4±2.0	7.5±2.6	0.0002
FBS (mg/dl)	130.8±17	128.5 ±25	0.4
S. T3 (nmol/L)	139.6±35.2	145± 40	.638
S. T4 (nmol/L)	8.5±2.3	10.5±2.3	.053
S. TSH (mU/L)	1.7±0.7	5±1.2	0.0001

The results presented in Table 4 indicate that both male and female participants in the case group had significantly higher mean HbA1c levels than those in the control group did. For males, the mean HbA1c level in the case group was significantly high (p = 0.00001), suggesting a strong association between the condition under investigation and increased HbA1c levels. In females, although the mean HbA1c level was also higher in the case group, the difference was less pronounced, as indicated by a p-value of 0.04. These findings highlight a significant relationship between condition and elevated HbA1c levels in both sexes, with the effect being more significant in males than in females.

Table 4. Effect of Gender on HbA1c Levels in Case and Control Groups. *p < 0.05 = Statistically Significant

Variable	Control	Case	*P*-value
Male	5.7±1.4	8± 2.7	0.00001
Female	5.9±1.8	6.9±2.2	0.04
P-value		0.04	

Discussion

In this study, the majority of both cases and controls were within the 18-50year age group. Additionally, there was a higher representation of females, who made up 53% (106 out of 200) of the total participants, compared to males, who accounted for 47% (94 out of 200).
Thyroid dysfunction is common in adults [19,20] The TSH test is the most effective primary tool for assessing thyroid function, and is the most dependable method for diagnosing primary hypothyroidism in outpatient settings [21,22]. In this study, serum TSH levels were significantly higher in individuals with subclinical hypothyroidism than in healthy controls, consistent with previous findings[23, 24].
Previous studies have reported a significant positive linear correlation between serum levels

of T3 and T4 and HbA1c, suggesting that these thyroid hormones may influence glycemic control [25, 26]. However, in contrast to these findings, our study did not detect any significant correlations between T3, T4, and HbA1c levels. Specifically, our regression analysis showed that the unstandardized coefficients for T3 and T4 were 0.007 (p = .274) and -0.083 (p = .432), respectively, indicating that these hormones did not significantly affect the HbA1c levels in our sample. In contrast, our results align with the findings of other studies, which reported a significant correlation between serum TSH levels and HbA1c [27, 28]. In our study, we also found a significant positive association between TSH and HbA1c levels, with an unstandardized coefficient of 1.801 (p = .002). This finding suggests that higher TSH levels, which indicate thyroid dysfunction, may be associated with elevated HbA1c levels, reinforcing the potential link between thyroid function and glycemic control.

These findings highlight the complexity of the relationship between thyroid hormone levels and glucose metabolism. Although T3 and T4 did not show a significant impact in our study, the strong association between TSH and HbA1c underscores the importance of considering thyroid function, particularly TSH levels, in the assessment of glycemic control. Further research is needed to explore the mechanisms underlying these relationships and determine whether these findings are consistent across different populations.

Various observational studies have reported interactions between hypothyroidism and diabetes [29, 30]. In this study, we found a highly significant increase in HbA1c levels in the non-diabetic SH group compared with the control group (p = 0.0002). The mean serum HbA1c level was within the normal range. Our findings support earlier research indicating that hypothyroidism can lead to increased HbA1c levels in both diabetic and non-diabetic individuals [31].This suggests that elevated HbA1c in hypothyroid patients might not solely reflect poor glycemic control but could also be influenced by thyroid dysfunction itself.

Conclusion

Based on the findings of the present study, we conclude that HbA1c levels significantly increase with elevated TSH levels in nondiabetic individuals. This suggests that the use of HbA1c as a diagnostic tool for diabetes in individuals with hypothyroidism may be less reliable. Therefore, additional diagnostic methods should be considered when assessing for diabetes in patients with hypothyroidism.

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