Correlation of circulating diabetes markers with elevated serum antithyroglobulin antibodies in type 2 diabetes patients

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ABSTRACT

A total of 250 males and females were recruited to participate in this cross-sectional and case-control study that aimed at measuring several biomarkers [fasting blood glucose (FBG), glycated hemoglobin (HbA1c), thyroid hormonal profile, and antithyroglobulin antibody (ATG)] in diabetic and non-diabetic patients and comparing circulating markers of diabetes mellitus with elevated serum ATG levels in type II diabetes patients who used various analyzers. The assays were performed on Roche COBAS C311, COBAS e 411/601, and Beckman Coulter (DXC 700 AU) analyzers. The mean and standard deviation were calculated, and the independent t-test and one-way analysis of variance were used for comparison. Linear regression was conducted to assess correlations. A p-value of <0.05 was considered statistically significant. This study included 125 diabetic patients compared with 125 healthy males and females, with ages ranging from 20 to 81 years and a duration of diabetes mellitus between 4 and 15 years. The results demonstrated a significant difference in FBG, HbA1c, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and ATG levels between the diabetic patients and the healthy individuals, compared to age, gender, and duration of the disease. A moderate positive correlation was observed between FBG and HbA1c, as well as between FT3 and FT4; a negative correlation was found between FBG and HbA1c levels and TSH levels. A significant positive correlation between ATG and serum TSH levels observed in patients with type 2 diabetes mellitus indicated a strong relationship between thyroid dysfunction and diabetes, compared to the age and duration of the disease.

Introduction

The relationship between thyroid disease (TD) and diabetes mellitus (DM) is complex. Both hypothyroidism and hyperthyroidism are more common in type 2 diabetes mellitus (T2DM) patients.[1,2] The presence of anti-thyroid peroxidase and anti-thyroglobulin antibodies (ATG) can explain the variation in TD prevalence.[3,4] TD can exacerbate subclinical DM and lead to hyperglycemia in T2DM patients. Additionally, T2DM patients have a more complex etiology than type 1 diabetes mellitus (T1DM) patients, but TD is more prevalent in T1DM patients.[5] The high incidence of anti-thyroid antibodies in T2DM patients suggests that thyroid dysfunction is likely to develop in the future in these individuals. Untreated or inadequately treated TD can negatively impact diabetes control.[6-8] Therefore, it is important to screen T2DM patients for TD and manage both conditions effectively to improve patient outcomes.[2,9] The prevalence of TD in diabetes patients varies depending on the study and the specific population. In general, the prevalence of TD in the general population is estimated to be 6.6%, with hypothyroidism being the most common issue.[10,11] In diabetic patients, the prevalence of thyroid dysfunction is higher, ranging from 13.4% to 14.7%.[4,12] The most common thyroid dysfunction in diabetic patients is subclinical hypothyroidism, which can negatively impact diabetes control and increase the risk of cardiovascular complications.[1]

Materials and Methods

A cross-sectional and case-control study was conducted at Thumbay Hospital, Ajman, on 250 participants, 125 diabetic and 125 non-diabetic patients, aged 20 to 81 years; the duration of DM ranged from 4 to 15 years; the gender distribution was 107 males and 143 females. The Institutional Review Board of Gulf Medical University, Ajman, approved this study and granted a license to collect research data from Thumbay Hospital (Ref. no. IRB/COHS/STD/86/DEC-2022). To ensure the confidentiality of research participants, the study adhered to all ethical guidelines set by the ethics committee. The specimen collected from both male and female diabetic and non-diabetic patients was used to conduct various biomarkers, including fasting blood glucose (FBG) and glycated hemoglobin (HbA1c). Blood samples were collected in fluoride-oxalate and whole-blood ethylenediaminetetraacetic acid tubes for the respective tests. The Roche COBAS C311 analyzer (F. Hoffmann-La Roche Ltd, Basel, Switzerland) was used to perform a UV test to detect glucose in blood serum and plasma, with glucose concentration measured spectrophotometrically at 340 nm. Additionally, thyroid function tests, including ATG, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4), were conducted using the COBAS 411/601 analyzer (F. Hoffmann-La Roche Ltd, Basel, Switzerland), which is an automated immunoassay system. The HbA1c samples were analyzed on a Beckman Coulter (DXC 700 AU) (Beckman Coulter Inc., Brea, CA, USA) using the immunoturbidimetric method. The validation procedure for the tests was done according to CAP and ECLIA for precision, accuracy, and linearity. The study and laboratory procedures described adhere to standard protocols for conducting and validating diagnostic tests. The use of specific analyzers and testing methods is in line with established practices in clinical laboratories. The results were analyzed by SPSS version 26 (IBM, Chicago, IL, USA). The mean and standard deviation were obtained, and *t*-independent, one-way analysis of variance, and Chi-square tests were used for comparison. Linear regression was used for correlation; a p-value was obtained to assess the significance of the results ($p<0.05$ was significant).

Results

The study was conducted on 250 participants (125 diabetic and 125 non-diabetic patients), aged 20 to 81 years, and with a duration of DM ranging from 4 to 15 years. The gender distribution was 107 males and 143 females; most of the patients had poor glycemic control. Gender differences revealed a greater percentage of females with good glycemic (68%) compared to males (64%). The patients in the 8-11 years duration category showed higher percentages of good control compared to other groups (Table 1).

The mean of FBG levels in diabetic patients was 115.5±35.1 mg/dL, and in non-healthy individuals, FBG was 109 mg/dL, with a mean of 97.7±33.1 mg/dL; the difference between the two groups was statistically significant (p=0.001).

HbA1c mean levels in diabetic patients were 6.96±1.95%, and in non-diabetic individuals, it had a mean of 5.32±1.29%; the difference in HbA1c between the case and control groups was statistically significant (p=0.016).

Diabetic patients' ATG levels ranged from 387 to 3120 IU/mL, with a mean of 2155.4±54.2 IU/m, while healthy individuals' ATG levels ranged from 413 to 3533 IU/mL, with a mean of 1351.7±38.1 IU/m; there was a significant difference in ATG means between the two groups (p=0.012).

Table 1. Association of diabetes duration and glycemic control with age and gender demographics.

Demographic variable		Age group						Gender			
		Young aged		Middle-aged		Old-aged		Males		Females	
		N	%	N	%	N	%	N	%	N	%
Duration of diabetes disease	4-7 years	0	0	11	7	26	18	21	14	29	19
	8-11 years	0	0	25	17	39	26	33	22	36	24
	12-15 years	9	5	17	12	24	15	19	13	12	8
Glycemic status %	Good	12	7	53	36	39	26	97	64	102	68
	Poor	4	2	19	13	23	16	53	36	48	32

The TSH mean levels in diabetic patients were 1.98±1.27 mIU/L, whereas the TSH mean levels in non-diabetic individuals were 2.05±1.05 mIU/; this difference was significant between the groups (p=0.009).

Diabetic patients' FT3 mean was 1.61±0.52 pmol/L and non-diabetic individuals' FT3 mean was 1.45±0.35 pmol/L; the differences in FT3 levels between diabetic and non-diabetic individuals were significant (p=0.008).

FT4 levels in diabetic patients had a mean of 114±0.77 pmol/L and in non-diabetic individuals, FT4 levels had a mean of 107±0.24 pmol/L; the results demonstrated a significant difference in the mean of FT4 (p=0.038).

These results revealed a significant difference in biomarker levels between diabetic and non-diabetic individuals. From these results, significant differences were observed in the means between FBG (126.5±33.7, 113.4±39.7, 111.9±38.5 mg/dL) and the durations of diabetes disease (4-7 years, 8-11 years, 12-15 years, respectively) (p=0.027) and a statistically significant difference was observed in HbA1c levels (p=0.007), with the highest levels observed in the 8-11 years group. The results revealed a significant difference in the means of the thyroid hormonal profile (TSH, FT3, FT4, and ATG) compared with the duration of the diabetes disease (4-7, 8-11, and 12-150 years with respectively p=0.011, p=0.05, p=0.041 and p=0.048) (Tables 2 and 3). The scatter matrix correlation revealed a significant relationship between the thyroid hormones, FBG, and HbA1c levels. TSH and FBG showed a weak negative correlation (R=-0.34, p=0.001), and FT3 and FT4 presented moderate positive correlations with FBG (R=0.54, p=0.03; R=0.46, p=0.029, respectively). A weak negative correlation was observed between TSH and HbA1c (R=-0.27, p=0.02), while both FT3 and FT4 demonstrated moderate positive correlations with HbA1c (R=0.36, p=0.004; R=0.33, p=0.028) (Figures 1 and 2).

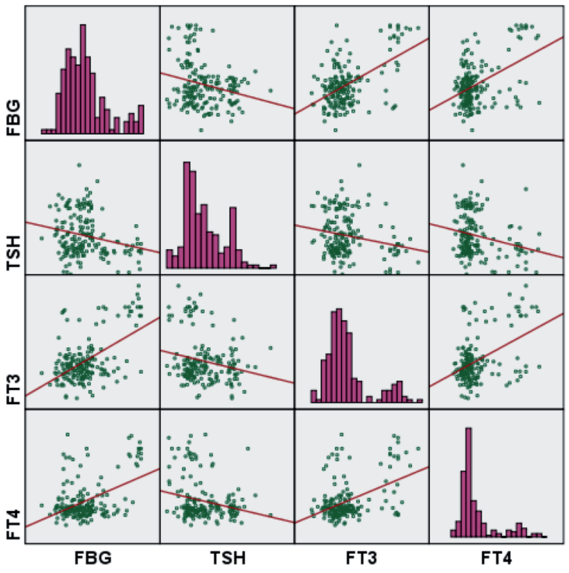

Figure 1. Scatter matrix correlation between thyroid-stimulating hormone (THS), free triiodothyronine (FT3), free thyroxine (FT4) and fasting blood glucose (FBG) levels. TSH/FBG: R=(-0.34), p=0.001; FT3/FBG: R=(0.54), p=0.03; FT4/FBG: R=(0.46), p=0.029. R is the correlation coefficient used to measure how strong a relationship is between two variables; a p-value <0.05 was considered significant.

Table 2. Comparison of biomarker levels between diabetic and non-diabetic individuals

Biomarkers	Diabetic		Non-diabetic		p
	Range	Mean±SD	Range	Mean±SD	
FBG mg/dL	101-291	115.5±35.1	71-109	97.7±33.1	0.001
HbA1c %	5.8-15	6.96±1.95	3.1-5.5	5.32±1.29	0.016
ATG IU/mL	387-3120	2155.4±54.2	413-3533	1351.7±38.1	0.012
TSH mIU/L	0.09-8.61	1.98±1.27	0.02-4.13	2.05±1.05	0.009
FT3 pmol/L	0.83-3.80	1.61±0.52	0.46-2.60	1.45±0.35	0.008
FT4 pmol/L	91.2-206	114±0.77	79.2-221	107±0.24	0.038

Independent *t*-test was used to obtain p-values; p<0.05 (significance). SD, standard deviation; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; ATG, antithyroglobulin antibody; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

Table 3. Comparison of circulating biomarkers across different durations of diabetes.

Duration of diabetes disease	Circulating markers, mean ± SD					
	FBG mg/dL	HbA1c %	TSH mIU/L	FT3 pmol/L	FT4 pmol/L	ATG IU/mL
4-7 years	126.5±33.7	6.6±1.05	2.40±1.48	1.68±0.65	123±0.32	123±0.32
8-11 years	113.4±39.7	7.1±2.21	2.03±1.38	1.54±0.53	113±0.19	2365.7±69.2
12-15 years	111.9±38.5	6.96±2.06	1.65±0.95	1.67±0.50	110±0.15	2243.5±66.2
p	0.027	0.007	0.011	0.05	0.041	0.048

One-way analysis of variance was used to obtain p-values; p<0.05 (significance). SD, standard deviation; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; ATG, antithyroglobulin antibody; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

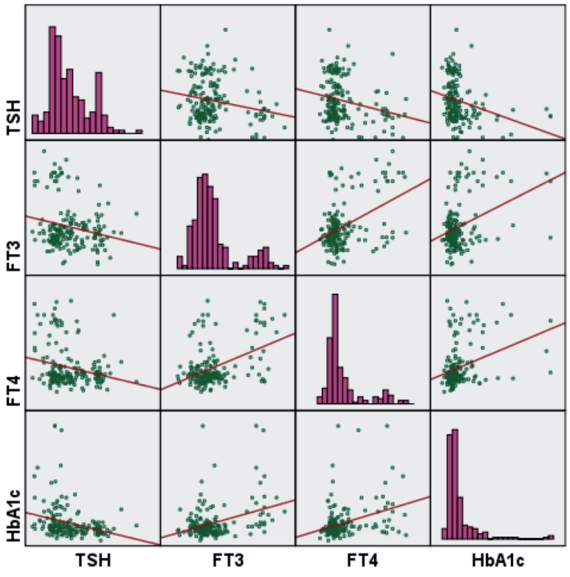

Figure 2. Scatter matrix correlation between thyroid-stimulating hormone (THS), free triiodothyronine (FT3), free thyroxine (FT4), fasting blood glucose levels and glycated hemoglobin (HbA1c) levels. TSH/HbA1c: R=(-0.27), p=0.02; FT3/HbA1c: R=(0.36), p=0.004; FT4/HbA1c: R=(0.33), p=0.028. R is the correlation coefficient used to measure how strong a relationship is between two variables; a p-value <0.05 was considered significant.

Discussion

Diabetes impaired thyroid function by altering TSH levels and the conversion of thyroxine to triiodothyronine in peripheral tissues.[13] Thyroid disorders are significantly more prevalent in T2DM patients, and there is evidence of a strong relationship between TD and diabetes. TD and diabetes both involve hormonal changes, and there is growing evidence that suggests a relationship between the two conditions.[14,15] Thyroid disorders can affect blood glucose levels, and an imbalance in thyroid hormones makes it more difficult to manage diabetes. The study revealed that, aligning with existing studies on the relationship between T2DM and TD, most of these studies focus on the impact of diabetes on thyroid function and the potential implications for disease management.[16] TD and T2DM are closely associated with hyperthyroidism. Several studies have documented the increased prevalence of thyroid disorders in patients with T2DM; both hypothyroidism and hyperthyroidism are more frequent in T2DM patients.[17] As a consequence of hyperthyroidism, the insulin levels decrease, and blood sugar rises, increasing the risk of diabetes. In this study, low TSH and high FT3/FT4 are associated with a greater risk of developing Graves' disease, and the possibility of developing T2DM increases in a dose-dependent manner with TSH level fluctuation.[18] The study confirmed the significant association between hyperthyroidism and T2DM. Different underlying mechanisms that affect glucose homeostasis in hyperthyroidism may be related to increasing blood glucose levels and shortening the half-life of insulin, which speeds up the breakdown of insulin and increases the production of physiologically inactive insulin precursors. In conclusion, the research supported the close association between thyroid dysfunction and T2DM,[19,20] with various studies focusing on the impact of thyroid hormones on glucose metabolism and the increased prevalence of thyroid disorders in T2DM patients. Further prospective studies are needed to fully understand the complex relationship between thyroid function and the risk of developing T2DM.[17,21,22]

Conclusions

A significant positive correlation between ATG and serum TSH levels had been observed in patients with T2DM, indicating a strong relationship between thyroid dysfunction and diabetes compared to the age and duration of the disease.

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