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Association between thyroid abnormalities & glycemic control among adults with type 1 Diabetes Mellitus: Cross-sectional study in Saudi Arabia

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Abstract

Background: The type 1 diabetic population has an increased incidence of thyroid dysfunction, accounting for approximately 17-30%. Thyroid dysfunction may interfere with insulin sensitivity and insulin requirements in individuals who have type 1 diabetes. This study aimed to find an association between thyroid function and poor glycemic control among adults with type 1 diabetes mellitus using TSH and HbgA1C, respectively.

Methods: A cross-sectional study was conducted in King Abdulaziz Medical City, Riyadh – Kingdom of Saudi Arabia (a tertiary hospital). Our subjects were adults with type 1 diabetes mellitus who had their TSH levels tested, between 2015 to 2019. Patients were categorized based on their TSH level as either hypothyroid, hyperthyroid, or normothyroid. The following variables were measured: patient's demographics, Thyroid-stimulating hormone level, the presence of anemia, WBCs, LDL level, and history of diabetic ketoacidosis.

Results: There were a total of 1425 adult patients with T1DM between 2015 and 2019, only 282 patients fulfilled our inclusion criteria. 36.2% were males (N=102) and 63.8% were females (N=180). The patients' mean age was 27.03 years with an average BMI of 25.62 kg/m2. 18.4% were hypothyroid and 9.9% were hyperthyroid. Our subjects had a mean HbA1c of 8.76%. hyperthyroid patients had higher HbA1c levels with a mean of 8.907 while hypothyroid patients had a mean of 8.11%. Also, we have found that patients with hyponatremia tend to have poor glycemic control in comparison to hypernatremia and normal serum sodium. We found that age, TSH, having a history of diabetic ketoacidosis and serum sodium to be significantly associated with HbA1c with P-values of 0.016, 0.012, 0.005 and <0.001 respectively.

Conclusion: Thyroid dysfunction was observed in a high proportion of our patients. We have found a clear association between thyroid function and glycemic control among adults with type 1 diabetes mellitus. Glycemic

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control was better among hypothyroid patients compared to hyperthyroid and normothyroid patients. Also, glycemic control is poor in hyponatremia in comparison to hypernatremia and normal serum sodium patients. HbA1C was significantly associated with age, TSH, serum sodium, and having a history of diabetic ketoacidosis but not with gender, body mass index and LDL level.

.**Keywords:** Glycated hemoglobin, hyperthyroid, hypothyroid, Thyroid-stimulating hormone, Saudi Arabia.

1. Introduction

Type 1 diabetes mellites (T1DM) is an autoimmune disease that is described as progressive destruction of insulin-secreting pancreatic beta cells, primarily by effector T-cells [1]. It is characterized by profound insulin deficiency requiring exogenous insulin. The term HbA1c refers to glycated hemoglobin that is formed when hemoglobin combines with glucose [2,3]. The thyroid gland produces thyroid hormones under the influence of thyroid stimulating hormone (TSH) from the anterior pituitary gland [4]. The prevalence of T1DM globally, according to WHO, is estimated as 19.4 million cases with an estimated increase in incidence reaching approximately 57.2 million by the year 2025 [2]. Locally, in the Kingdom of Saudi Arabia, the incidence of T1DM in 2018 was approximately estimated to be 33.5 cases per 100,000 sample (0.0335%), and the total T1DM cases were approximately 35,000 in both children and adolescents [5]. Owing to the autoimmune nature of T1DM, it is associated with several organ specific autoimmune diseases, the most common of which is autoimmune thyroid disease [6]. To emphasize, Thyroid pathologies are common among T1DM, accounting for 17-30% [7]. The reported percentage of TSH abnormalities according to a recent study account for approximately 10%, and 5% of women who will have either hypothyroidism or hyperthyroidism [8]. To clarify, a study was conducted on 40 randomly selected T1DM patients and their first-degree relatives (FDR). The results have proved that there were abnormal TSH levels in T1DM patients and their FDRs in the percentage of approximately 8% to 25%. It has been found that there is no association between TSH levels and age, ethnicity, or gender [9]. Another study has stated that diabetic patients have a higher risk to develop thyroid disorders since they have an autoimmune disease, which is diabetes, it has claimed that the most reliable test to detect thyroid disorder is immunoassay for serum TSH [10]. A third study has claimed that thyroid dysfunction may interfere with insulin sensitivity and insulin requirements in individuals who have type 1 diabetes [11].

Although most of the available literature focused on the association between T1DM and thyroid diseases, few focused on the effect of TSH on glycemic control among T1DM patients. We believe that a more in-depth review is needed to better understand the association between TSH and glycemic control in type 1 diabetics, using HbgA1C, with age, BMI, LDL, history of DKA, and serum sodium level.

Through deeper and more comprehensive of this association, we would be able to early detect the associated conditions, such as hyper/hypothyroidism and hyper/hyponatremia. However, if there is no association, it would indicate that further testing is not required.

2. Subjects and Methods

A retrospective cross-sectional study was conducted in the endocrinology department of King Abdulaziz Medical City, Riyadh Saudi Arabia.

The study subjects were adults who were diagnosed with type 1 diabetes mellitus and have had their serum TSH tested between 2015 and 2019. We had a total of 1425 patients, only 282 patients have fulfilled our inclusion criteria. We excluded patients with conditions or medications that could potentially alter TSH level, such as patients on amiodarone or patients diagnosed with pituitary adenomas.

The data got extracted from patient's electronic records after receiving the IRB approval from King Abdullah International Medical Research Center, KAIMRC. All those patients who did TSH level testing were taken, afterward, the status of the TSH was labeled as normal or abnormal and made in the initial groups. Then further grouping was done based on the TSH status if hypo or hyper. Microsoft Excel was used to store patients' data. The main dependent variable in the study is HbA1c percentage. The other independent variables include TSH level leading to thyroid status (either hypo or hyper), Serum Sodium levels, gender, age, and BMI.

Management and entry of the data were carried by Microsoft Excel; however, analysis of the data was carried by SPSS 27. Descriptive analysis was carried out to assess the relationship between TSH abnormalities and HbA1c. The grouping variable was thyroid status either hypothyroidism or hyperthyroidism depending on TSH levels. Categorical data such as gender is presented as frequencies and percentages, while numerical data like age, BMI, TSH levels, are presented as mean ± standard deviation. ANOVA test was used to assess the association between HbA1c and gender, age. BMI, TSH levels, anemia, LDL level, DKA, and Serum Sodium levels, respectively. Then Tukey test was used for significant findings of ANOVA test.

3. Results

There was a total of 282 patients who fulfilled our inclusion criteria between 2015 and 2019. The males were 36.2% (N=102), and the females were 63.8% (N=180). Patients with the age between 18 to 20 were 18.1% (N=51), between 21 and 30 were 54.6% (N=154), and more than 31 were 27.3% (N=77), and the average age was 27.03 years and standard deviation of 7.310. Underweight patients were 7.8% (N=22), normal weight 43.1% (N=121), overweight 29.9% (N=84), obese were 19.2% (N=54), and the average BMI was 25.62 kg/m2. Patients with hyperthyroidism (Low TSH level) were 9.9% (N=28).

Table (1): Demographic data of the study groups

		Count	Column N %
Gender	Male	102	36.2
	Female	180	63.8
Age (years)	18 -20	51	18.1
	21 - 30	154	54.6
	31+	77	27.3
Body mass index groups	Underweight	22	7.8
	Normal weight	121	43.1
	Overweight	84	29.9
	Obese	54	19.2
TSH	Normal	202	71.6
	Hyperthyroidism	28	9.9
	Hypothyroidism	52	18.4
Anemia	Yes	79	28.0
	No	203	72.0
LDL	Normal	91	32.3
	Hyperlipidemia	184	65.2
	NA	7	2.5
WBCs	Normal	244	87.1
	Leukocytosis	23	8.2
	Leukopenia	13	4.6
DKA	No history	145	51.4
	History	110	39.0
	NA	27	9.6
Na	Normal	142	50.4
	Hypernatremia	3	1.1
	Hyponatremia	137	48.6

Patients with hypothyroidism (High TSH level) were 18.4% (N=52). Patients who had normal TSH levels were the majority, accounting for 71.6% (N=202). Patients who had a history of Diabetic Ketoacidosis (DKA) were 39% (N=110), those who did not 51.4% (N=145), and those whose data

regarding DKA was not available (NA) accounted for 9.6% (N=27). Patients with hypernatremia were 1.1% (N=3), patients with hyponatremia were 48.6% (N=137), and those with normal serum sodium were 50.4% (N=142). Hyperlipidemic patients (high LDL) were 65.2% (N=184), those with normal LDL were 32.3% (N=91), and the ones who were NA were 2.5% (N=7). (Table 1)

Table (2) Mean and std. Deviation

	Minimum	**Maximum**	**Mean**	**Std. Deviation**
Age	18	61	27.03	7.310
weight	36.0	133.0	66.163	15.9801
Height	130.0	190.0	160.604	8.6605
HbA1C	5.5	15.9	8.766	1.8855
Body mass index	14.42	51.56	25.6226	5.76387

The mean HbA1c among our population was 8.76%, with a minimum of 5.5%, and with a maximum of 15.9%. (Table 2) By using ANOVA test our results have shown that there is a significant association between HbA1c and age with the p-value of 0.016. By using Tukey after the ANOVA, we found the major difference lies between the age group of 18 – 20 and >31 with the significance of 0.027 and the difference between the age group of 21 – 30 and >31 with the significance of 0.038.

Moreover, there is a significant association between HbA1c and TSH with the P-value of 0.012. The significant was mainly between the normal TSH patients and the ones with hypothyroid with a significance of 0.009. Also, our results have shown a significant association between HbA1c and serum sodium levels with a p-value of <0.001. The main difference was between normal serum sodium levels and patients with hyponatremia with <0.001 significance. Furthermore, our results have proven that there is significance between HbA1c and having a history of DKA with a p-value of 0.005 between having a history and not having a history of DKA. (Table 3)

Table (3) ANOVA Results

Variable	**Category**	**HbA1C**				
		Number	Percentage	Mean	SD	P-value
Gender	Male	102	36.2	8.8	2.1	0.978
	Female	180	63.8	8.8	1.7	
Age (years)	18 -20	51	18.1	9.1	2	0.016
	21 - 30	154	54.6	8.9	2	
	31+	77	27.3	8.3	1.5	
Body mass index groups	Underweight	22	7.8	9.7	2.1	0.07

	Normal weight	121	43.1	8.8	1.9	
	Overweight	84	29.9	8.6	1.8	
	Obese	54	19.2	8.5	2	
TSH	Normal	202	71.6	8.9	1.9	0.012
	Hyperthyroidism	28	9.9	8.9	2.3	
	Hypothyroidism	52	18.4	8.1	1.3	
Anemia	Yes	79	28.0	8.8	2.1	0.79
	No	203	72.0	8.7	1.8	
LDL	Normal	91	32.3	8.6	1.8	0.66
	Hyperlipidemia	184	65.2	8.8	1.9	
	NA	7	2.5	8.6	2.9	
WBCs	Normal	244	87.1	8.7	1.8	0.124
	Leukocytosis	23	8.2	9.5	2.1	
	Leukopenia	13	4.6	8.6	2.2	
DKA	No history	145	51.4	8.6	1.8	0.005
	History	110	39.0	9.2	2.1	
	NA	27	9.6	8.1	1.4	
Na	Normal	142	50.4	8.3	1.5	<0.001
	Hypernatremia	3	1.1	8.6	0.6	
	Hyponatremia	137	48.6	9.3	2.1	

Furthermore, we have noticed that patients with hypothyroid have better glycemic control than hyperthyroid and normothyroid patients. (Figure 1)

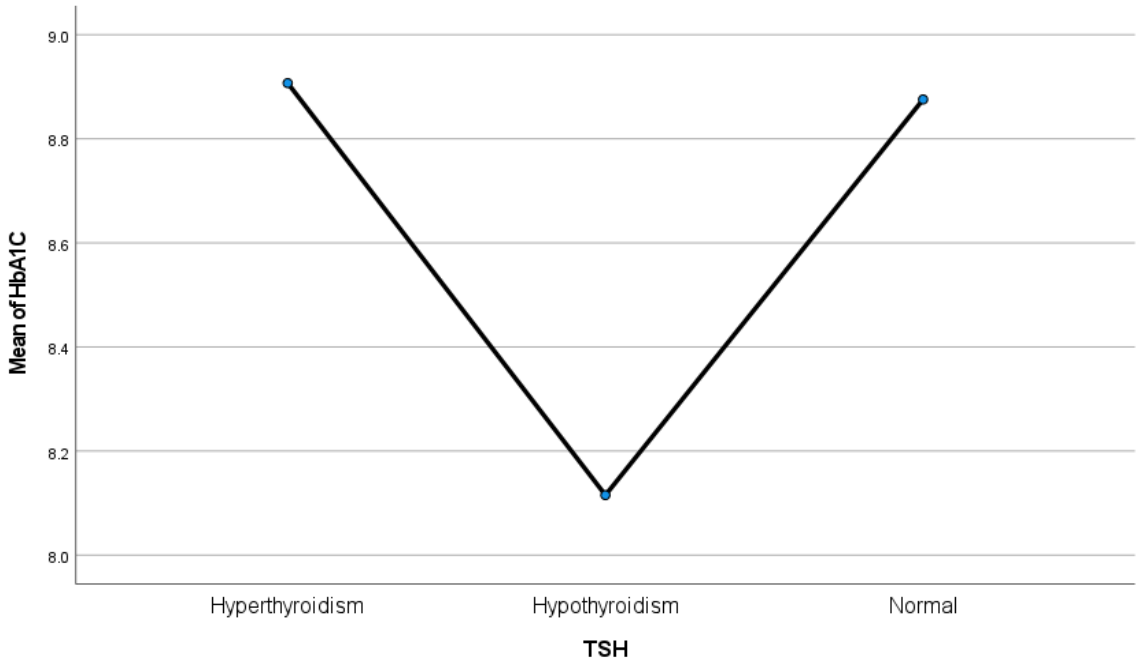

Figure 1: TSH on glycemic control means plot

In addition, we have found that patients with hyponatremia tend to have poor glycemic control in comparison with hypernatremia and patients with normal serum sodium. (Figure 2)

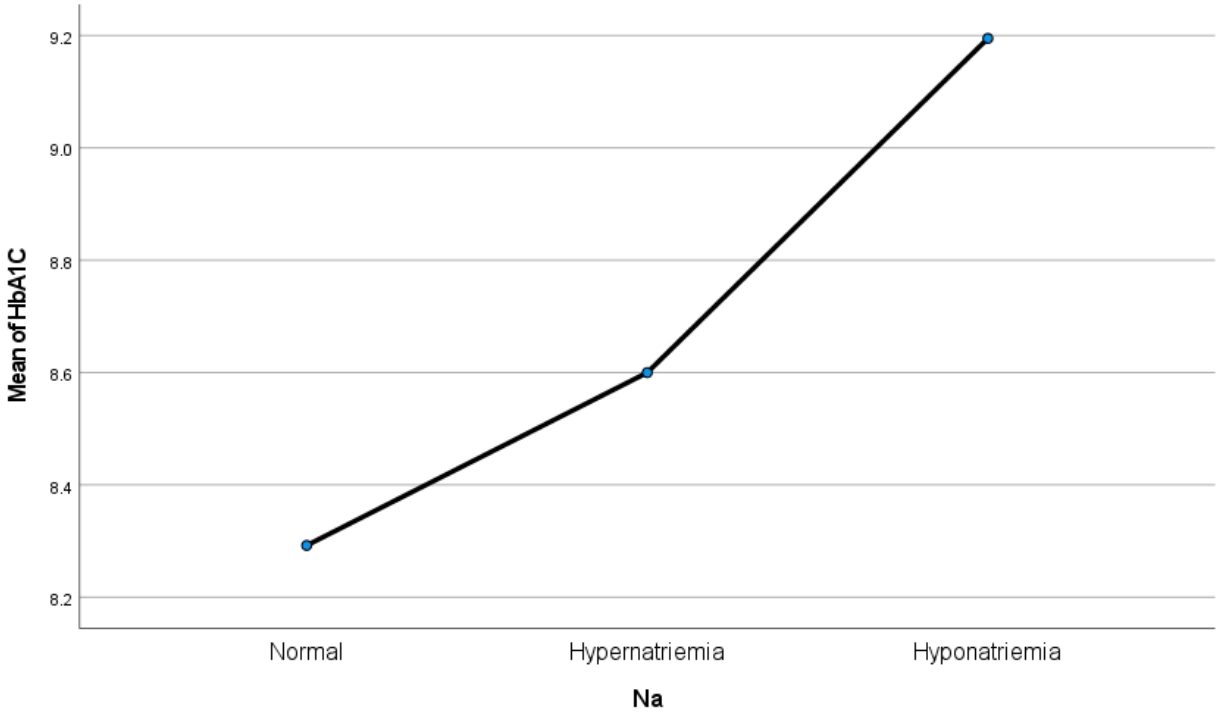

Figure 2: Serum sodium status effect on glycemic control means plot

4. Discussion

The link between T1DM and thyroid dysfunction has been well established [9-12] The majority of the reported literature related to this topic were focused on T1DM and thyroid autoimmunity in pediatrics and adolescents, barely any have looked at poor glycemic control in adults with T1DM and thyroid function. In the current study, we investigated the association between thyroid function and poor glycemic control among adults with type 1 diabetes mellitus using TSH and HbgA1C, respectively.

Our subjects were adults with poorly controlled T1DM with a mean HbgA1C of 8.76%. We found that 28.3% of them have thyroid dysfunction, most of which were attributed to hypothyroidism. This percentage is within the upper limit of what was reported in the literature [6]. Scientifically, this finding can be explained by A. ROGOWICZ-FRONTCZAK et al, who addressed the bridge between insulin resistance induced by long-standing poorly controlled T1DM and thyroid pathologies [13].

In our study, hypothyroidism was observed the most and accounted for 18.4%. Indeed, this is in agreement with other previously published studies [14-15]. Metwalley KA et al, have found similar results but in a different age group that is children and adolescents [15]. In contrast to Metwalley KA et al, we found an inverse proportion between HbA1C and TSH level. To clarify, the mean HbA1C among hypothyroid patients, in our study, was 8.11%, while hyperthyroid patients had a mean of 8.907%. This

is logical and well-established in the literature due to the fact that hyperthyroidism can precipitate hyperglycemia by increasing the dietary absorption of glucose and hepatic secretion. On the other hand, hypothyroidism can potentially prolong insulin action and reduce hepatic secretion which points toward lower glucose level [16].

In the present study, we found that having a previous history of DKA is significantly associated with HbA1C (P 0.005). This is especially true in hypothyroid patients. Few studies have discussed thyroid status in T1DM who had DKA at initial presentation [17-18]. Lin et al. demonstrated significantly lower thyroid hormone levels among children with newly diagnosed T1DM who presented with DKA compared to those without DKA [17]. Fatourechi et al, also have reported a more aggressive T1DM and higher DKA rates at presentation in those with hypothyroidism [19]. Although these studies have investigated this matter in pediatrics, we believe adults have the same implications.

Our study has not found an association between HbA1C and gender, body mass index, and LDL level. This is in accordance with M. Rodacki et al, who discussed the TSH effect on chronic complications of T1DM. To emphasize, in their study, high TSH level was associated with a higher risk of diabetic retinopathy and renal failure regardless of glycemic control [11]. In our study, we have noticed a significant relation between HbA1C and serum sodium, particularly hyponatremia ($P < 0.001$), which may be explained as a complication of poor glycemic control.

Our study was a single centered retrospective cross-sectional study with a relatively small sample size and some missing data. We have not included variables that could potentially affect HbA1C and/or TSH, such as hemoglobinopathies, pregnancy, and medications. We believe that a more in-depth review is needed to better understand the effect of thyroid dysfunction on both the course and insulin requirements in T1DM. To achieve this, large multi-centered studies are required.

The results have shown a significant association between HbA1C levels with TSH status, serum sodium levels, and history of DKA among Type 1 adult Diabetic patients. We recommend doing periodic TSH screening to detect thyroid abnormalities and to rule out hypothyroidism. Also, doing serum sodium screening is necessary to check for hyponatremia. Hyponatremia and hypothyroidism affect HbA1c levels, so both of which are supposed to get treated accordingly.

5. Conclusion

In this study, we explored the prevalence of TSH abnormalities among type 1 diabetes mellitus adult patients. We found that hypothyroid patients tend to have lower HbA1c levels than patients who have hyperthyroid and normothyroid. Moreover, there are high HbA1C levels in patients with hyponatremia compared to patients with high and better serum levels. (Figures 1 and 2) Also, we have

found an association between HbA1c with age and having a history of DKA. There was no association between HbA1c with gender, body mass index, and LDL levels. We recommend periodic TSH and serum sodium for type 1 diabetic patients who have high HbA1c.

6. Declarations

6.1 Conflict of Interest Statement

The authors have no conflict of interests to declare.

6.2 Funding Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.3 Ethical Considerations:

The ethical approval was taken from institutional review board of King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia. All the participants information was kept confidential.

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