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Research Article

Relationship Between Glycemic Control and Thyroid Function Among Patients with Type 2 Diabetes Mellitus

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Abstract

Background and Objective

The association between diabetes and thyroid dysfunction were reported. Thus, the present study was conducted to find out the relation between glycemic status and levels of thyroid hormones in type 2 diabetes mellitus (T2DM) in a cohort of Saudi population.

Design

A cross-sectional study was conducted in the Diabetes centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia from January 2018 to December 2018. Thyroid stimulating hormone (TSH), free thyroxin (FT4) and HbA1c were measured.

Results

A total of 1168 participants with T2DM were included in this study. Average age of the study population was 55.1 ±16.2 years. 31.7% were male and 68.3% were female. Mean HbA1c (%), TSH and FT4 were 7.4 ±2, 3.3 ±4.8mIU/l and 13.7 ±3.2pmol/L respectively. TSH was statistically significant higher in patients with HbA1c≥7 compared to patients with HbA1c<7 (p=0.02) with statistically non-significant difference between males and females. FT4 was statistically significant lower in patients with HbA1c≥7 compared to patients with HbA1c<7 (p=0.009) with statistically significant higher FT4 in females compared to males in patients with HbA1c<7 (p=0.01). Age and HbA1c were the independent predictors of TSH level. In the constructed model, HbA1c was found to be an independent predictor of TSH level (P=0.048). HbA1c level was found to be an independent predictor of serum FT4 level (P=0.03).

A statistically significant positive correlation was observed between TSH and HbA1c (r = 0.060, P = 0.04). Also, a significant negative correlation was observed between FT4 and HbA1c (r = -0.068, P = 0.03).

Conclusion

Poor glycemic control is associated with abnormal thyroid hormones in cohort of Saudis with T2DM. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true relation nationally.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder [1]. The prevalence of DM has been increasing at alarming rates all over the world and is estimated to rise to 552 million adults by 2030 [2]. Saudi Arabia is the seventh of the top ten countries in terms of the prevalence of diabetes among the adult population [3].

Thyroid disorders are also very common in the general population and it is second only to DM as the most common condition to affect the endocrine system [4,5]. Type 2 diabetes mellitus (T2DM) and thyroid diseases tend to co-exist together and thyroid diseases are more common in DM than in general population [6,7]. The association between T2DM and thyroid dysfunction were first published in 1979 [8]. Various studies have estimated the prevalence of thyroid disorder in diabetic patients, in few studies higher prevalence in T2DM has been estimated [9,10].

Altered thyroid hormones have been described in patients with DM especially those with poor glycemic control. T2DM may affect thyroid function either at the level of hypothalamic control of thyroid stimulating hormone (TSH) release or at the conversion of thyroxine (T4) to triiodothyronine (T3) in the peripheral tissue. It has been well documented that hyperglycemia leads to reversible reduction of the activity and hepatic concentration of T4-5-deiodinase, which leads to low serum concentration of T3 and low, normal, or high levels of T4 [11].

Although related to glycemic control, the pathophysiology of thyroid hormone alterations in patients with T2DM has never been fully investigated. In some conditions, T2DM is related to abnormal thyroid function, involving very low glucose level in the blood and also renal disorders [12,13]. The presence of T2DM is also related to the insufficiency of the replacement of thyroid hormone in elderly patients with hypothyroidism [14]. Several studies have been conducted to find out the prevalence of thyroid dysfunction in diabetic patients but only few studies have compared the levels of thyroid hormone with glycemic status in diabetic patients. The present study is carried out to find out the inter relation between the glycemic status and levels of thyroid hormones in T2DM.

Methods

A cross-sectional study was conducted in the Diabetes centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia between January 2018 to December 2018 for a period of 12 months which included 1168 patients who were diagnosed as T2DM on the basis of ADA criteria [15]. Patients who are pregnant were excluded. TSH was measured with a chemiluminescent immunoassay method (CMIA) (Architect i2000 system, Abbott, USA). Serum free thyroxine (FT4) was estimated by radioimmunoassay. The assays have intra- assay precision of 4.3%. TSH levels between 0.22-4.2mIU/L and Free T4 12.0-22.0pmol/L were regarded normal [16]. High performance liquid chromatography was used. HbA1c was expressed as percentage.

Statistical Analysis

Data are presented as means ± standard deviation (SD) or numbers (%). Quantitative variables were compared between two groups by using the Student's test. Differences in categorical variables were analyzed using the chi-square test. The relationship between continuous variables was assessed using coefficients of correlation. Multivariate linear regression model was constructed using TSH and FT4 as the dependent variables and factors with either a P-value less than 0.15 in the univariate analysis or a previously reported association with either TSH or FT4 as independent variables. Null hypotheses were rejected where p values were less than 0.05. Logistic regression analysis was carried out to estimate odds ratio (OR) and 95% CI. P value <0.05 indicates significance. The statistical analysis was conducted with SPSS version 23.0 for Windows.

Results

A total of 1168 participants with T2DM were included in this study. Average age of the study population was 55.1 ±16.2 years (table 1). 31.7% were male and 68.3% were female. Mean HbA1c (%), TSH and FT4 were 7.4 ±2, 3.3 ±4.8mIU/l and 13.7 ±3.2pmol/L respectively. TSH was statistically significant higher in patients with HbA1c≥7 compared to patients with HbA1c<7 (p=0.02) (figure 1) with statistically non-significant difference between males and females (figure 2). FT4 was statistically significant lower in patients with HbA1c≥7 compared to patients with HbA1c<7 (p=0.009) (figure 3) with statistically significant higher FT4 in females compared to males in patients with HbA1c<7 (p=0.01)(figure 4).

Table 1: *Base line characteristic of total population*

Parameters		Total(1168)
Age (years)		55.1 ±16.2
Gender	Male	370 (31.7)
	Female	798 (68.3)
HbA1c (%)		7.4 ±2.0
TSH (mIU/l)		3.3 ±4.8
FT4 (pmol/l)		13.7 ±3.2

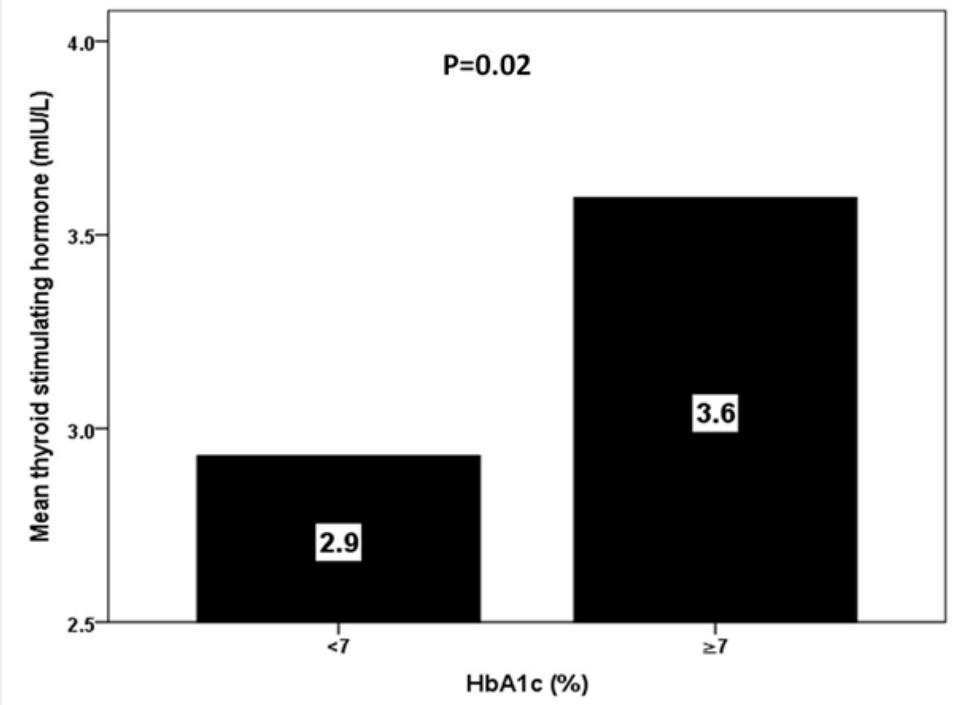

Figure 1: *Mean thyroid stimulating hormone (mIU/L) in relation to HbA1c (%) groups*

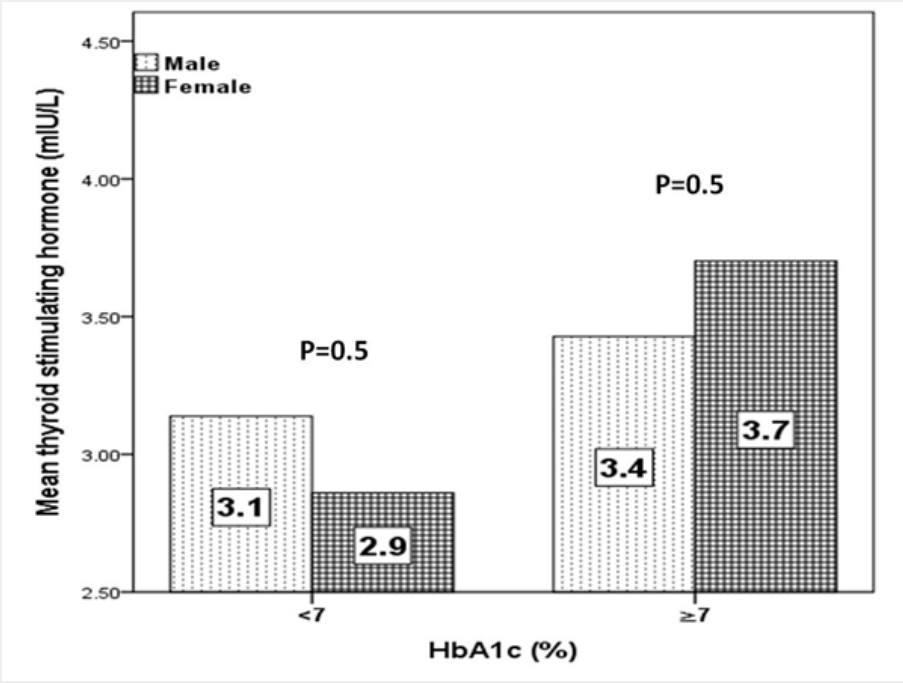

Figure 2: *Mean thyroid stimulating hormone (mIU/L) in relation to HbA1c (%) groups correlated to gender*

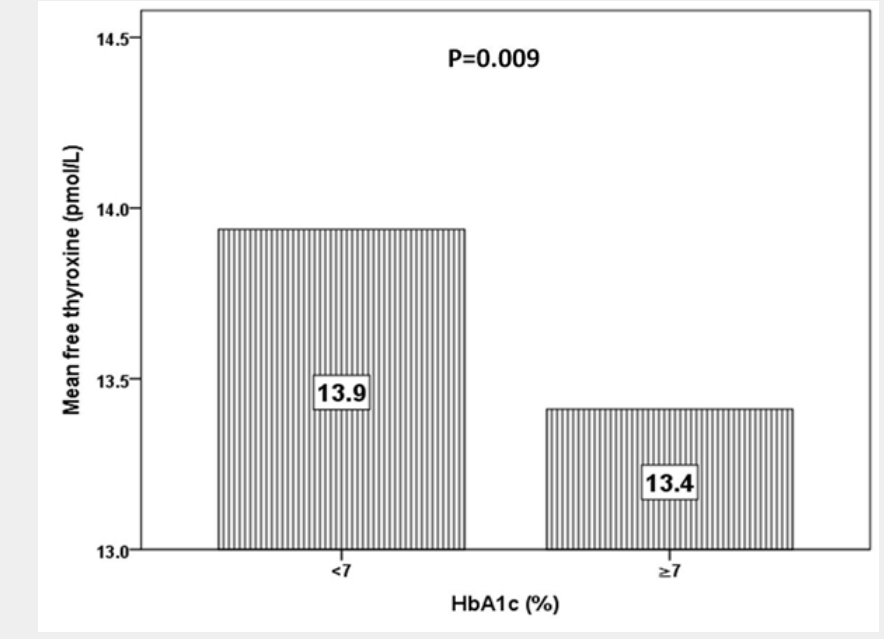

Figure 3: *Mean free thyroxine (pmol/L) in relation to HbA1c (%) groups*

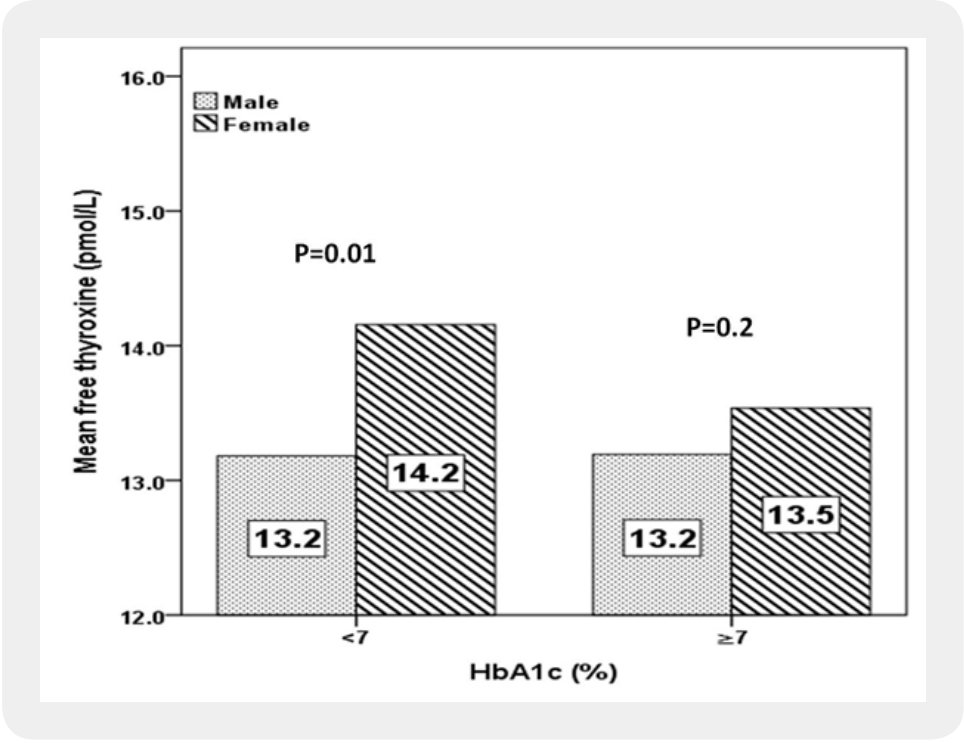

Figure 4: *Mean free thyroxine (pmol/L) in relation to HbA1c (%) groups correlated to gender*

In order to identify the independent factors affecting TSH level, a multivariate linear regression model was constructed using the serum TSH concentration as the dependent factor. The constructed model is shown in Table 2. Age and HbA1c were the independent predictors of TSH level. In the constructed model, HbA1c was found to be an independent predictor of TSH level (P=0.048).

Table 2: *Linear regression analysis using serum concentrations of TSH as the dependent variable.*

Parameters	Coefficients	Std. Error	95% Confidence interval	P value
Age (years)	0.006	0.009	-0.011-0.023	0.5
HbA1c (%)	0.137	0.069	0.001-0.272	0.048

The second linear regression model using serum FT4 level as the dependent variable was performed with age and HbA1c as independent variables (Table 3). In the constructed model, HbA1c level was found to be an independent predictor of serum FT4 level (P=0.03).

Table 3: *Linear regression analysis using serum concentrations of FT4 as the dependent variable*

Parameters	Coefficients	Std. Error	95% Confidence interval	P value
Age (years)	0.006	0.009	-0.008-0.017	0.5
HbA1c (%)	-0.113	0.051	-0.212- (-0.013)	0.03

A statistically significant positive correlation was observed between TSH and HbA1c (r = 0.060, P = 0.04) (Figures 5). Also, a significant negative correlation was observed between FT4 and HbA1c (r = -0.068, P = 0.03) (figure 6).

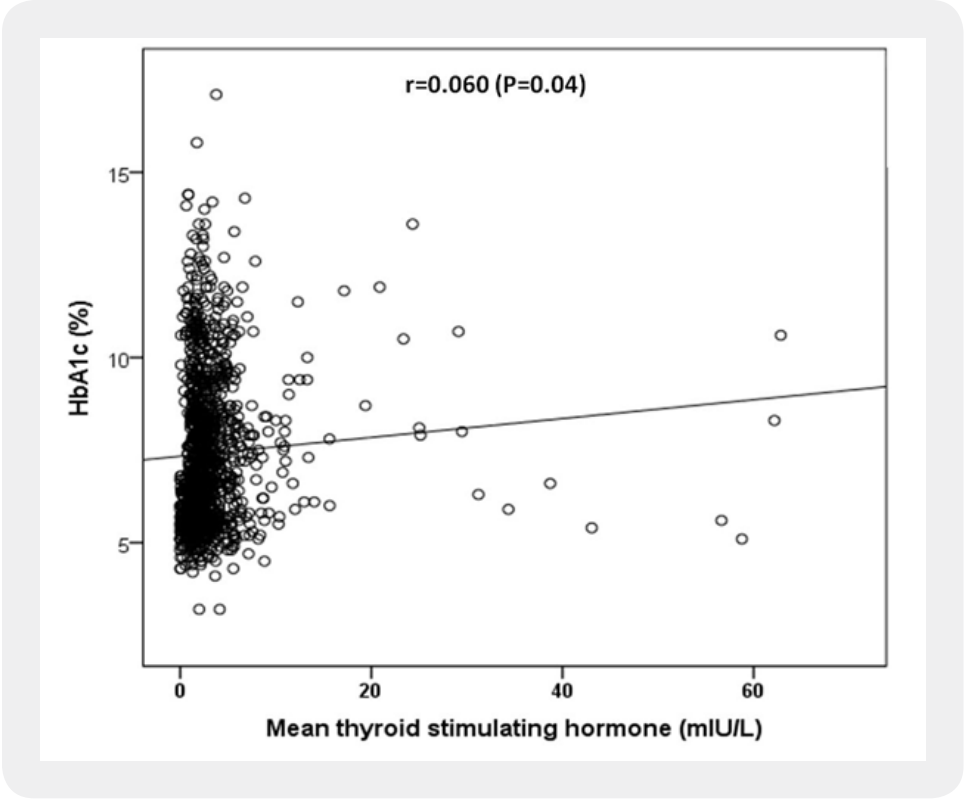

Figure 5: *Correlation of thyroid stimulating hormone concentration (mIU/L) and HbA1c (%)*

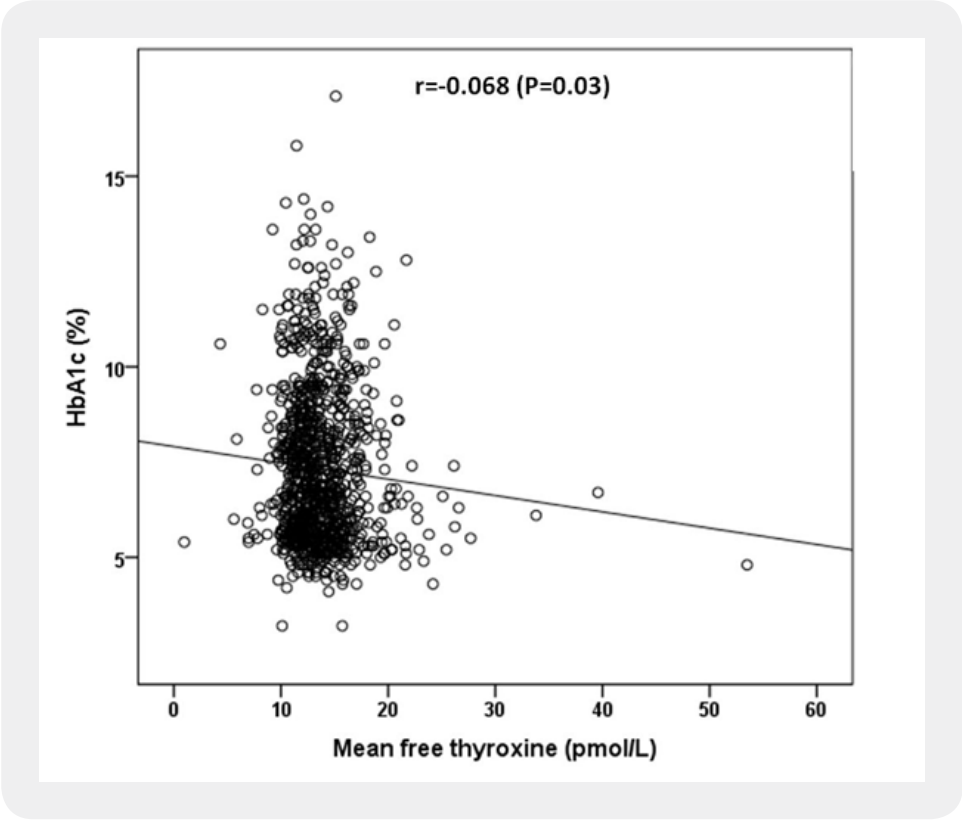

Figure 6: *Correlation of free thyroxine (pmol/L) concentration and HbA1c (%)*

Discussion

Since the measurement of HbA1c levels is important not only for monitoring of T2DM, the results of our study showed an obvious association between elevation of HbA1c levels and high TSH and low FT4 in patients with T2DM in corroboration with others [17,18]. Previous studies reported that T2DM do not affect FT4, therefore observed normal level of FT4 in diabetic patients when compared with reference range, hypothesize that medication of T2DM may influence the thyroid hormone profile thus observed normal results of FT4 [19]. However, our observation on the variation in TSH level is in harmony with the results of Cappelli *et al.* and in contrast to other [19,20]. These differences appear to be also due to DM medications Furthermore, the result of correlation test showed a positive correlation between HbA1C and TSH in T2DM, these observations are consistent with previous studies Udiong *et al.* who reported significant association between HbA1C and TSH [21]. In contrast the results of HbA1c and FT4 showed significantly negative correlation, this finding was disagreed with studies performed by Saha *et al.*which showed no correlation between HbA1c and FT4 among diabetic patient with T2DM [18,20].

In our study, there was a raised mean TSH levels in diabetics with HbA1c ≥7 as compared to <7. These findings were supported by the study of Uppal *et al* who reported raised mean TSH levels in diabetics as compared to controls with a non-significant p value [22]. Other studies like Moura-Neto *et al* and Islam *et al*

have found the same results with a non-significant p value [23,24]. Some other studies like Farasat *et al,* Saha *et al* and Bharat *et al* showed a significantly raised TSH lev-els in diabetics as compared to healthy controls [25-27]. These findings were contrary to the study done in Calabar, Nigeria by Udiong *et al* in 2007 on diabetics and healthy controls [28]. They have found a low mean TSH level in diabetics as compared to healthy controls.

In the present study, there was a significant lower serum FT4 levels in diabetics with HbA1c ≥7 as compared to <7. This finding is in discordance with others [25,29,30]. Farasat *et al* reported that patients with T2DM had significantly raised serum T4 levels as compared to controls with a p value of 0.02.25 But our findings are in accordance to the findings of Uppal *et al* who conducted a study on 120 diabetics and 117 healthy controls [22] They found a low serum T4 levels in diabetics as compared to controls but with a non-significant p value. Moura-Neto *et al* conducted a study on 52 diabetics and 52 healthy controls [23]. They found a low serum total thyroxine (TT4) level in diabetics as compared to healthy controls (p=0.006). Other studies also observed a low TT4 levels in diabetics as compared to healthy controls [12,31,32].

It has been suggested that altered thyroid status in T2DM is linked toleration of hypothalamo-pituitary-thyroid axis causing decreased formation of TT4. Also there is less activation of AMPK (5'-Adenosine Mono Phosphate activated Protein Kinase) in T2DM that also causes decreased formation of thyroid hormones [33]. Decrease levels of thyroid hormones cause increased TSH release from anterior pituitary gland by feedback mechanism [13,27,34] Most of the T2DM patients were obese who might have increased level of leptin. This increased level of leptin develops leptin resistance centrally that causes decreased formation of thyroid hormones and increase TSH secretion [33]. Moreover the binding affinity of TT4 is increased in T2DM that causes decrease formation of FT4 in blood. [13,27]. T2DM are also associated with obesity, stress, infection that caused changes in hypothalamo-pituitary thyroid axis lead to decrease level of FT4 and increased TSH level in T2DM [33] The hyperglycaemia seen in patients with T2DM is known to have negative effect on thyroid function precisely blunting the pituitary TSH response to stimulation by hypothalamic TRH. This may be due to possible alteration of post translational glycosylation of TRH hence affecting its biological activity [35]. T2DM is associated with increased insulin level and C-peptide level. Insulin is an anabolic hormone known to enhance TSH turnover, which is protein in nature. Recently, C-peptide has been shown to enhance Na+/K+- ATPase activity, an action that may also increase protein synthesis. Such an action would induce increased turnover of TSH, a protein hormone [36,37].

Our results showed a non-statistically significant different levels between thyroid hormones in diabetics with HbA1c ≥7 as compared to <7 in both males and females. Still, detailed molecular mechanisms remain unclear, because sex hormones (such as estrogen, and testosterone) can regulate the thyroid function [38]. The difference in sex hormones may partly explain the sex-difference in the relationship between thyroid hormone levels. However, because levels of sex hormones such as testosterone and estrogen were not measured in this study, further research is needed to explore this issue. In addition, because the sample size was smaller for males (31.7%) than in females (68.3%), the precision and statistical power of the analysis may be lower for males. Further large-scale population studies are required to confirm the above findings.

We aimed to identify the relation between HbA1c and TSH and FT4 levels in patients with T2DM in hospital-based health care setting. Furthermore, due to the cross sectional nature of this study, the observed population reflects a selected yet comprehensive group of patients rather than the general population. In addition, the current study population may appear limited in size and therefore may underestimate the true relation between HbA1c and TSH and FT4 levels in patients with T2DM.

Conclusions

We conclude that despite the limitations of this hospital-based cross sectional study, poor glycemic control is associated with abnormal thyroid hormones in cohort of Saudis with T2DM. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true relation nationally.

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