

## The Relation of Glycemic Control and Hyperthyroidism in Saudi Patients with Type 2 Diabetes Mellitus

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### Abstract

**Background and Objective:** The association between diabetes and hyperthyroidism were reported. Thus, the present study was conducted to find out the relationship between glycemic control and hyperthyroidism in Saudi patients with type 2 diabetes mellitus (T2DM).

**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 1669 subjects with T2DM were included in this study. Average age of the study population was  $51.4 \pm 16.2$  years. 25.1% were male and 74.9% were female. Mean HbA1c (%), TSH and FT4 were  $7.4 \pm 2.0$ ,  $1.8 \pm 1.1$  mIU/l and  $14.2 \pm 5.3$  pmol/L respectively. Hyperthyroidism (HT) and subclinical hyperthyroidism (SCH) were present in 2.0% and 7.5% respectively where HT was non-statistically significant younger than SCH and euthyroid patients ( $p = 0.5$ ). Moreover, females were statistically significant more prevalent than males ( $p = 0.002$ ). HbA1c was statistically significant lower in HT compared to SCH or euthyroid patients (6.2, 6.8 and 7.5 respectively,  $p = 0.007$ ).

The frequency of HbA1c  $< 7\%$  compared to HbA1c  $\geq 7\%$  was significant higher in HT and SCH and lower in euthyroid patients ( $p = 0.04$ ). There was a statistically significant differences between gender and HbA1c % groups in correlation to thyroid dysfunction ( $p < 0.0001$ ) whereas males with HbA1c  $\geq 7\%$  in SCH patients were statistically significant higher than females ( $p = 0.04$ ). There was a statistically significant differences between age groups above and below 50 years and HbA1c % groups in correlation to thyroid dysfunction ( $p < 0.0001$ ) whereas there was non-statistically significant difference between age groups and Hba1c  $\geq 7.0\%$  in patients with HT and SCH ( $P = 0.2$  and  $p = 0.4$  respectively).

**Conclusion:** Poor glycemic control was not associated with more prevalent of HT and SCH.

**Keywords:** Hyperthyroidism; Glycemic Control and Type 2 Diabetes Mellitus

### Introduction

Diabetes being the most common endocrine metabolic disorder, there was curiosity to understand and learn the association of this with another common endocrine gland function that is thyroid gland. Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. The association between these two disorders has long been recognized although the prevalence of the thyroid dysfunction in diabetic population varies widely between studies [1,2]. With insulin and thyroid hormone being intimately involved in cellular metabolism, excess or deficit of one of these hormones result in functional derangement of the other enhanced sensitivity and specificity of thyroid stimulating hormone (TSH) has greatly enhanced assessment of thyroid dysfunction [3].

The prevalence of thyroid disease in the diabetic patients is significantly higher than in the general population [4]. Apart from autoimmune etiology linked to the higher prevalence of thyroid disease in diabetes mellitus; it has also been observed that thyroid function is intrinsically linked to insulin resistance. It has also been stated that common factors simultaneously are responsible for increased TSH levels and insulin resistance [5]. In type 2 diabetes mellitus (T2DM), prevalence of thyroid disease has been found to be as high as 31%, the most common disorder being subclinical hypothyroidism, followed by subclinical hyperthyroidism, overt hypothyroidism and overt hyperthyroidism [6]. Thyroid function tests done in a study population of 298 Type 2 diabetics conducted by Nobre., *et al.* in 2002, in Europe showed that 38 (12.7%) of them suffered from thyroid dysfunction. 2% had hyperthyroidism [7]. In a study sample of 100 Type 2 diabetics at Chennai, the prevalence of TD was found to be 15% with 2%, subclinical hyperthyroidism and 1% hyperthyroidism [8].

In euthyroid individuals with diabetes mellitus, the serum tri-iodothyronine (T3) levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status [9]. Poorly controlled diabetes in patients with T2DM may induce a "Low T3 state" characterized by low serum total and free tri-iodothyronine (T3) levels, increase in reverse T3 (rT3) but near normal serum thyroxine (T4) and TSH concentrations [9]. Low serum T3 is due to reduced peripheral conversion of T4 to T3 via 5' monodeiodination reaction [10]. Studies indicate that it may be the long-term diabetic control that determines the plasma T3 levels. Regardless of glycemic control, there is an absence of nocturnal TSH peak. Variable glucose intolerance is seen in up to 50% of patients with hyperthyroidism. and frank diabetes occurs in 2 - 3%, when hyperthyroidism develops in normal individuals. In known diabetic patients, the diabetic control deteriorates [10]. Varied metabolic changes may occur as a result of hyperthyroidism and contribute to the deterioration of glycemic control status. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal absorption of glucose, and probably increased insulin resistance also. Indeed, thyrotoxicosis may unmask latent diabetes [4].

Few studies have been conducted to find out the prevalence of hyperthyroidism in patients with T2DM but only very few studies have compared the levels of glycemic status with hyperthyroidism in patients with T2DM. The present study is carried out to find out the inter relation between hyperthyroidism and glycemic status in patients with T2DM in a cohort of Saudi population.

### Methods

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 for a period of 12 months which included 1669 patients who were diagnosed as T2DM on the basis of ADA criteria [11]. Patients who are pregnant were excluded. Thyroid stimulating hormone (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 - 4.2 mIU/L and Free T4 12.0 - 22.0 pmol/L were regarded normal [12]. High performance liquid chromatography was used. HbA1c was expressed as percentage. The participants were then divided as hyperthyroid (HT), subclinical hyperthyroid (SCH) and euthyroid depending on the thyroid profiles. HT was defined as TSH < 0.22 mIU/l and increased serum levels of FT4 above the reference range whereas SCH was defined as TSH < 0.22 mIU/l and normal serum levels of FT4. The total number of cohort were separated on basis of age values into two groups: < 50 years and ≥ 50 years.

### 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. Differences in mean serum 25-OHD levels were tested with ANOVA. The relationship between continuous variables was assessed using Spearman coefficients of correlation. The statistical analysis was conducted with SPSS version 23.0 for Windows.

### Results

A total of 1669 subjects with T2DM were included in this study. Average age of the study population was 51.4 ± 16.2 years (Table 1). 25.1% were male and 74.9% were female. Mean HbA1c (%), TSH and FT4 were 7.4 ± 2.0, 1.8 ± 1.1 mIU/l and 14.2 ± 5.3 pmol/L

respectively. HT and SCH were present in 2.0% and 7.5% respectively where HT was non-statistically significant younger than SCH and euthyroid patients ( $p = 0.5$ ) (Table 2). Moreover, females were statistically significant more prevalent than males ( $p = 0.002$ ). HbA1c was statistically significant lower in HT compared to SCH or euthyroid patients (6.2, 6.8 and 7.5 respectively,  $p = 0.007$ ).

Parameters		Total (1669)
Age (years)		51.4 ± 16.2
Gender	Male	419 (25.1)
	Female	1250 (74.9)
HbA1c (%)		7.4 ± 2.0
TSH (mIU/l)		1.8 ± 1.1
FT4 (pmol/l)		14.2 ± 5.3

Table 1: Base line characteristic of total population.

Variable		Hyperthyroidism	Subclinical hyperthyroidism	Euthyroid	P values
Numbers		33 (2.0)	125 (7.5)	1411 (90.5)	
Age (years)		49.1 ± 14.8	50.4 ± 13.6	51.5 ± 16.4	0.5
Gender	Male	3 (9.1)	19 (15.2)	397 (26.3)	0.002
	Female	30 (90.9)	106 (84.5)	1114 (73.7)	
HbA1c (%)		6.2 ± 1.4	6.8 ± 1.8	7.5 ± 2.0	0.007
Thyroid stimulating hormone (mIU/l)		0.05 ± 0.06	0.09 ± 0.07	2.0 ± 1.0	< 0.0001
Free thyroxine (pmol/l)		30.0 ± 14.0	15.5 ± 3.1	13.7 ± 4.4	< 0.0001

Table 2: Characteristic of patients according to HbA1c (%) [mean ± standard deviation or number (%)].

The frequency of HbA1c < 7% compared to HbA1c ≥ 7% was significant higher in HT and SCH and lower in euthyroid patients ( $p = 0.04$ ) (Figure 1). There was a statistically significant differences between gender and HbA1c % groups in correlation to thyroid dysfunction ( $p < 0.0001$ ) whereas males with HbA1c ≥ 7% in SCH patients were statistically significant higher than females ( $p = 0.04$ ) whereas Males with HbA1c ≥ 7% in SCH patients were statistically significant higher than females ( $p = 0.04$ ) (Figure 2). There was a statistically significant differences between age groups above and below 50 years and HbA1c % groups in correlation to thyroid dysfunction ( $p < 0.0001$ ) whereas there was non-statistically significant difference between age groups and Hba1c ≥ 7.0% in patients with HT and SCH ( $P = 0.2$  and  $p = 0.4$  respectively).

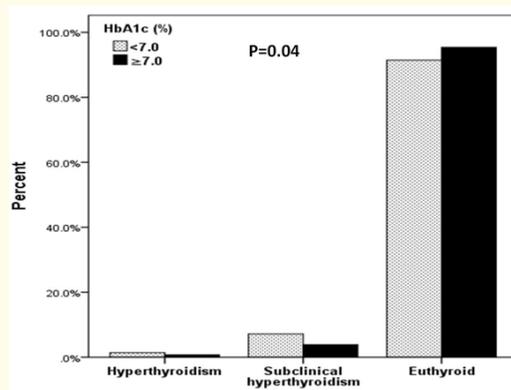


Figure 1: Prevalence of hyperthyroidism in relation to HbA1c categories.

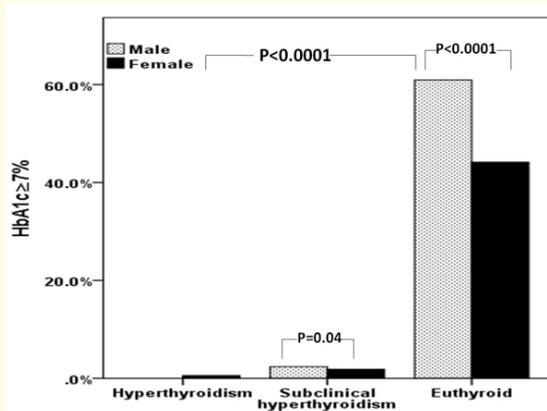


Figure 2: Prevalence of hyperthyroidism between gender in relation to HbA1c categories.

A non-statistically significant positive correlation was observed between TSH and HbA1c in the total population ( $r = 0.024, P = 0.4$ ). Also, a non-statistically significant positive correlation was observed between TSH and HbA1c (%) in patients with HT ( $r = 0.271, P = 0.4$ ). Moreover, a non-statistically significant negative correlation was observed between TSH and HbA1c (%) in patients with SCH ( $r = 0.105, P = 0.4$ ).

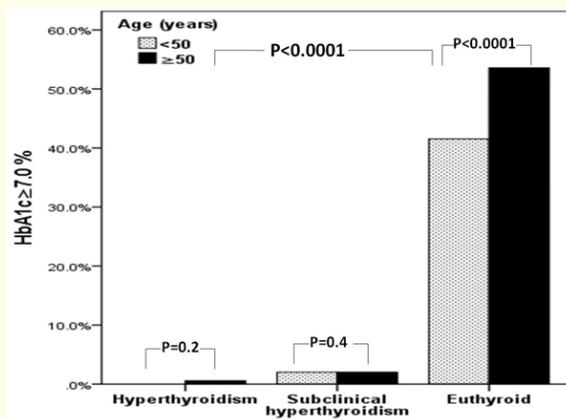


Figure 3: Prevalence of hyperthyroidism between HbA1c categories in relation to age distribution.

### Discussion and Conclusion

Among the endocrinal metabolic diseases diabetes occupies the major share. There is a complex interaction between thyroid dysfunction and diabetes mellitus [4,7,8,13-15]. In the present study among the 1669 subjects with T2DM, HT and SCH were present in 2.0% and 7.5% respectively. Poor glycemic control was not associated with more prevalent of HT and SCH. Thyroid function tests done in a study population of 298 Type 2 diabetics conducted by Nobre., *et al.* in 2002, in Europe showed that 2% had hyperthyroidism [7]. In a study sample of 100 Type 2 diabetics at Chennai, they found the prevalence of HT and SCH were 2% and 1% respectively [8]. In a study sample of 100 Type 2 diabetics in India, the prevalence of HT was found to be 5% with 1% was SCH [13]. Udiong., *et al.* studied 161 (18 Type 1 and 143 type 2) diabetic patients and found that prevalence of hyperthyroidism was 19.9% [14]. Moreover, a study from the United States reported that hyperthyroidism was found in 12% [4].

In our study we found that patients with uncontrolled T2DM, HbA1c  $\geq 7$  when compared to patients with HbA1c  $< 7$ , have statistically significant lower prevalence of HT and SCH (1.4 vs. 0.7%) and (7.2 vs. 3.9%) respectively,  $p = 0.04$ . Insulin and thyroid hormones, both act on cellular metabolism of carbohydrates, proteins and lipids. T2DM alters thyroid function at two sites. First T4-5-deiodinase activity and concentration are reduced by hyperglycemia. Second hypothalamic control of TSH is altered [16]. The knowledge of relation between thyroid disease and diabetes is of importance to guide clinicians on the optimal management of both these conditions. Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and increased insulin resistance [17].

The presence of both raised and low levels of thyroid hormones in diabetic may be due to modified thyrotropin releasing hormone (TRH) synthesis and release [14]. The hyperglycaemia seen in type 2 diabetics 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 [18]. 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<sup>+</sup>/K<sup>+</sup>-ATPase activity, an action that may also increase protein synthesis. Such an action would induce increased turnover of TSH, a protein hormone [19,20]. Reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation, gluconeogenesis, diminished hepatic glucose output and reduced disposal of glucose are hallmarks of hypothyroidism [21]. In overt or subclinical hypothyroidism, insulin resistance leads to glucose-stimulated insulin secretion [22]. In subclinical hypothyroidism, diminished rate of insulin stimulated glucose transport rate caused by perturbed expression of glucose transporter type 2 gene translocation may lead to insulin resistance. 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 by feedback mechanism in T2DM [23].

Our results showed a statistically significant higher prevalence of females in patients with HT and SCH. Still, detailed molecular mechanisms remain unclear, because sex hormones (such as estrogen, and testosterone) can regulate the thyroid function [24]. 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 (25.1%) than in females (74.5%), 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.

Our result showed a non-statistically significant positive correlation between HbA1c and TSH in the total cohort, HT and SCH. Uppal, *et al.* correlated the levels of insulin and HbA1c with thyroid hormones and reported that the levels of HbA1c have a positive and significant correlation with TSH level [25].

We aimed to identify the relation of glycemic control and HT and SCH in Saudi patients 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 of glycemic control and HT and SCH in patients with T2DM.

We conclude that despite the limitations of this hospital-based retrospective study, HT and SCH are not associated with poorly controlled Saudis patients with T2DM. More longitudinal cohort studies are needed to give high level of evidence to confirm this association in order to establish the need to be more aggressive in risk factor control in these individuals. More population based studies with large sample size needed in future; various geographical areas and populations should be considered.

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### Funds for Study

Nil.

### Conflict of Interest

None.

### Bibliography

1. Feely J and Isles TE. "Screening for thyroid dysfunction in diabetics". *British Medical Journal* 1.6179 (1979): 1678.
2. Gray RS., et al. "Screening for thyroid dysfunction in diabetics". *British Medical Journal* 2.6202 (1979): 1439.
3. Satish R and Moha V. "Diabetes and Thyroid disease: a review". *International Journal of Diabetes in Developing Countries* 23.4 (2003): 120-123.
4. Wu P. "Thyroid disease and diabetes". *Clinical Diabetes* 18.1 (2000): 38-41.
5. Fernández-Real JM., et al. "Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects". *Journal of Clinical Endocrinology and Metabolism* 91.9 (2006): 3337-3343.
6. Celani MF, et al. "Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus". *Diabetes Research* 27.1 (1994): 15-25.
7. Nobre EL., et al. "Profile of the thyroid function in a population with Type 2 diabetes". *Endocrine Abstracts*3 (2002): 298.
8. Lotz H and Salabè GB. "Lipoprotein(a) increase associated with thyroid autoimmunity". *European Journal of Endocrinology* 136.1 (1997): 87-91.
9. Schlienger JL., et al. "Effect of diabetic control on the level of circulating thyroid hormones". *Diabetologia* 22.6 (1982): 486-488.
10. Donckier JE. "Endocrine diseases and diabetes". In: Text book of Diabetes mellitus. Pickup JC, Williams G (eds), Blackwell Publishing Company, Chichester (2003): 27.1-27.25.
11. American Diabetes Association. "Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019". *Diabetes Care* 42.1 (2019): S13-S28.
12. dos Remedios LV, et al. "Detecting unsuspected thyroid dysfunction by the free thyroxine index". *Archives of Internal Medicine* 140.8 (1980): 1045-1049.
13. Papanna JJ and Bettegowda S. "Thyroid dysfunction among type 2 diabetes mellitus patients: A study from rural hospital". *Journal of Medical Science and Clinical Research* 7.4 (2019): 433-436.
14. Udiong CEJ., et al. "Evaluation of thyroid function in diabetes mellitus in Calabar, Nigeria". *Indian Journal of Clinical Biochemistry* 22.2 (2007): 74-78.
15. Amouzegar A., et al. "Tehran Thyroid Study (TTS)". *International Journal of Endocrinology and Metabolism* 16.4 (2018): e84727.
16. Pasupathi P. "Screening for thyroid dysfunction in the diabetic/nondiabetic population". *Thyroid Science* 3.8 (2008): CSL1-CSL6.

17. Lambadiari V, *et al.* "Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes". *Endocrine* 39.1 (2011): 28-32.
18. Suresh DR, *et al.* "Inter-relationship of glycemic control and thyroid status in type-2 diabetes mellitus". *International Journal of Clinical and Diagnostic Research* 2.4 (2014): V.
19. Bassyouni A, *et al.* "Profile of the thyroid function and ultrasound among patients with type-2 diabetes mellitus". *Science Medical Journal* 22.2 (2010): 15-28.
20. Shaikh AW, *et al.* "Frequency of hypothyroidism in type 2 diabetic patients". *Pakistan Journal of Medical and Health Sciences* 3.4 (2009): 298-301.
21. Althausen TL and Stockholm M. "The influence of the thyroid gland on absorption in the digestive tract". *The American Journal of Physiology* 123.3 (1938): 577-588.
22. Brenta G, *et al.* "Potential therapeutic applications of thyroid hormone analogs". *Nature Clinical Practice Endocrinology and Metabolism* 3.9 (2007): 632-640.
23. Kumar RA, *et al.* "Prevalence of thyroid dysfunction among type 2 diabetes subjects in south India". *Journal of Clinical Investigation* 5 (2014): 93-100.
24. Boucai L, *et al.* "An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits". *Thyroid* 21.1 (2011): 5-11.
25. Uppal V, *et al.* "Thyroid Disorders in Patients of Type 2 Diabetes Mellitus". *Indian Journal of Clinical Biochemistry* 28.4 (2013): 336-341.

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