

Evaluation of Thyroid Volume and Thyroid Function in Newly Diagnosed Type 2 Diabetes Mellitus Patients

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ABSTRACT

The pathophysiological relationship between thyroid dysfunction and diabetes mellitus (DM) is centered around the interplay between thyroid hormones and carbohydrate metabolism. The significance of thyroid dysfunction in type 2 DM is not fully recognised. This study investigated the effects of thyroid volume and thyroid function in newly diagnosed diabetic patients with the aim of recommending the significance of thyroid status assessment in the management of type 2 DM. One hundred patients newly diagnosed with type 2 DM and 100 non-diabetic volunteers were recruited for the study. Thyroid ultrasonography was used to measure thyroid volume and monitor presence of nodules. Thyroid function test was carried by analysing serum levels of free triiodothyronine (FT3), thyroxine (FT4) and thyroid-stimulating hormone (TSH) while severity of diabetic status was evaluated by measuring random blood sugar (RBS) and glycated hemoglobin (HbA1c). The prevalence of thyroid nodules, mean thyroid volume, RBS and HbA1c was significantly higher in the DM group compared to the non-DM group. With the exception of FT4, there was

no significant difference between the two groups in thyroid hormones. Pearson's correlation revealed strong uphill correlation between thyroid volume and RBS as well as HbA1c while the presence of thyroid nodules showed moderate downhill correlation with thyroid volume, RBS and HbA1c. Type 2 DM is associated with thyroid dysfunction that worsens with severity of diabetic condition, hence it is recommended that baseline and follow-up thyroid status be checked in newly diagnosed type 2 DM patients.

Keywords: Thyroid dysfunction, Diabetes Mellitus, Hyperthyroidism, Hypothyroidism, Insulin resistance.

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INTRODUCTION

Thyroid disease is an endocrine disorder commonly encountered in clinical practice, even though its prevalence varies among different populations. Previous studies have conducted an estimation of thyroid disease prevalence within different study populations at different times. For instance, the Wickham survey of 1977 published a prevalence of 6.6% among the adult population in the north of England (1), while 18.9% of a German population was reported to have thyroid dysfunction by a study conducted in 2016 (2). Globally, available data indicate that over 1.6 billion individuals may be at risk and would require some form of iodine supplementation (3).

Epidemiological data on thyroid dysfunction vary considerably due to differences in study design, conditions and target population. A recent cross-sectional study nested within the Birmingham Elderly Thyroid Study (BETS) reported 6% prevalence of subclinical thyroid dysfunction among the study population (4), whereas 17.2% prevalence of subclinical hypothyroidism and 1.2% subclinical hyperthyroidism was recorded in female patients with acute myocardial infarction (5). However, an overview of available data indicate that prevalence of subclinical hypothyroidism ranges between 4–25%, while overt hypothyroidism prevails in about 2–5% and are both higher in females above 60 years of age. Lower prevalence has been recorded for overt and subclinical hyperthyroidism averaging at about 0-4% and 1-2% respectively (6, 7).

Diseases of the thyroid are characterised by benign or malignant disorders affecting the structure and function of the thyroid gland which could lead to hypothyroidism, hyperthyroidism associated thyrotoxicosis, non-thyroid thyrotoxicosis, thyroid cancer and iodine deficiency disorders (IDDs) (8). Interestingly, studies have observed an increased frequency of thyroid dysfunction with advancing

age while women have shown a higher prevalence of thyroid disease compared to men (9, 10). Also, the incidence of thyroid dysfunction is higher in diabetic subjects compared to non-diabetics (11).

The interface between thyroid dysfunction and diabetes mellitus (DM) have been explored by previous studies. Reports have implicated thyroid dysfunction not only in the accretion of insulin resistance especially in type 2 DM, but also in complicating the management of diabetes (12).

Genetic studies have successfully identified the gene levels that could be used as

biomarkers in the prediction of metabolic syndrome (includes insulin resistance and hypertension) (13, 14). Although the direct link (genetic) between thyroid disease and type 1 DM has been well characterised, the genetic basis explaining the high frequency of thyroid disease in type 2 DM patients is just recently being established (15). Recent study however implicated homozygosity for polymorphism (Thr92Ala) of the deiodinase type 2 (DIO2) gene, in the risk of developing type 2 DM among pregnant women with thyroid disease (16). The indirect (metabolic) link between thyroid disease and type 2 DM have been long been predicated.

Since the thyroid hormones are involved in regulation of carbohydrate metabolism, it is expected that their abnormal levels would disrupt carbohydrate homeostasis. Hyperthyroidism leads to increase in the glucose turnover and gastrointestinal absorption that elevates hepatic glucose output, thereby increasing post-absorptive plasma glucose as well as insulin and pro-insulin levels. This raises the insulin requirement and onset of ketoacidosis coupled with an increased glucose uptake by peripheral tissues, as a result, peripheral insulin resistance sets in (11, 17). Hypothyroidism however, slows the absorption of glucose from the gastrointestinal tract and declines peripheral

glucose assimilation, hence, hepatic glucose output reduces and insulin secretion declines. This leads to a decreased peripheral glucose disposal which culminates into reduced peripheral utilisation of glucose and onset of insulin resistance (18, 19).

The ultrasonographical volumetric assessment of the thyroid gland (thyroid volume) has shown more precision in diagnosing thyroid dysfunction than clinical examination or palpation as it is widely used for diagnosis of goiter, follow-up evaluation after treatment of enlarged thyroid as well as other thyroid associated diseases (20, 21). Thyroid hormone imbalance have been reported in patients with Hashimoto thyroiditis as a result of increase in thyroid volume (22-24). Similarly, the association between thyroid volume and presence of thyroid nodules with metabolic syndrome has been previously established in an adult population (25). Thus, an abnormally large thyroid volume is indicative of a thyroid dysfunction.

However, whether thyroid volume-associated thyroid dysfunction is directly involved in the pathogenesis of type 2 DM or act as an effectuator in type 2 DM pathophysiology remains to be unraveled. The aim of this study was to highlight the relationship between thyroid volume, thyroid function and type 2 DM in newly diagnosed patients by evaluating the thyroid volume, thyroid nodule presence, thyroid hormone levels as they relate to diabetic indices of the type 2 DM patients in comparison with those of non-diabetics. This is to recommend optimal screening and assessment of thyroid status by clinicians, in the management of Type 2 DM.

MATERIALS AND METHODS

Study design

One hundred (100) patients, newly diagnosed with type 2 DM at Al-Hussein Teaching Hospital Kerbala, Iraq and 100 non-diabetic volunteers were included in the study.

Exclusion criteria include patients with type 1 DM or an established type 2 DM, pregnancy, complicated glycated haemoglobin (i.e. as a result of severe anemia or haemoglobinopathy) and patients on metformin for other reasons such as fatty liver or polycystic ovarian syndrome. The aim of the study was clearly stated to all subjects and written informed consent were obtained.

Blood samples were collected after a period of rest, with minimal occlusion of the vein. Random blood sugar (RBS) was measured using a pre-calibrated portable glucometer (CareTouch) and the American Diabetic Association guideline was adopted. Normal random blood sugar was defined as RBS \leq 140 mg/dL while participants with RBS \geq 200 mg/dL were defined as diabetics (26). Glycated hemoglobin (HbA1c) was measured using chromatographic- spectrophotometric ion exchange method by Genius diagnostic (Belgium) (27, 28). Normal range was defined as HbA1c between 4.2 – 6.2%, controlled diabetic was defined as HbA1c between 6.7 -91% while uncontrolled diabetic was defined as HbA1c $>$ 9.1% (28, 29).

Thyroid function was evaluated by analysing serum levels of free triiodothyronine (FT3), thyroxine (FT4) and thyroid-

stimulating hormone (thyrotropin, TSH) using Minividas compact multiparametric analyzer (USA).

Normal range for FT3 was 0.9-2.4 nmol/L, 9.0-21.0 pmol/L for FT4 and 0.2-4.5 mU/L for TSH (30).

The functional interpretation of thyroid function test was carried out as follows: Primary hypothyroidism was recognized if TSH was greater than 4.5 mU/L and FT3 and FT4 levels were lower than the normal range, subclinical hypothyroidism was recognised if TSH was between 5 and 20mU/L with free thyroid hormones in the normal range (31-33).

Primary hyperthyroidism was recognised if free thyroid hormones were raised and TSH was less than 0.2 mU/L while subclinical hyperthyroidism was recognized if TSH was less than 0.2 mU/L but free thyroid hormones are within the normal range (31-33).

Longitudinal and transverse ultrasound scan of the thyroid lobes using the Philips ClearVue 350 Ultrasound Machine (USA) was performed and measurements for depth (D), width (W) and length (L) were recorded. The volume (V) of each lobe was determined using the formula, $V \text{ (mL)} = D \text{ (cm)} \times W \text{ (cm)} \times L \text{ (cm)}/2$ (34), and total thyroid volume (TTV) was estimated from the sum of the volume of right and left thyroid lobes, the volume of the isthmus was not included. All measurements on thyroid in the study were conducted by a single investigator.

Statistical analysis was performed with the software program SPSS (version 24.0). All data were presented as mean \pm standard deviation and independent t tests was used to compare the status of the thyroid (volume and function) with changes in blood sugar levels between the two groups while Pearson's correlation was used to observe relationship between thyroid volume and diabetic indices. Statistical significance was set at p value $<$ 0.05.

This study was approved by the research and ethics committee of Al-Hussein Teaching Hospital, Kerbala.

RESULTS

The 100 newly diagnosed Type 2 DM patients (DM group) included in this study comprised of 44 males and 56 females with the mean age of 40.70 ± 8.02 years while the non-diabetic volunteers (non-DM group) comprised of 61 males and 39 females. As presented in Table 1, the prevalence of thyroid nodules among the study population was 64% for DM group which differed significantly from that of the non-DM group i.e. 29% prevalence. The mean thyroid volume of the DM group was 19.16 ± 4.52 mL and statistical significant difference ($p < 0.05$) was recorded when compared with the non-DM group having mean thyroid volume of 14.91 ± 2.95 mL. Significantly higher values for RBS and HbA1c were recorded in the DM group in relation to the non-DM group i.e. 282.30 ± 45.05 mg/dL (DM group) vs 93.38 ± 2.93 mg/dL (non-DM group) for RBS and 8.11 ± 1.93 % (DM group) vs 5.25 ± 0.22 % (non-DM group) for HbA1c. With the exception of FT4, which was 26.40 ± 5.27 pmol/dL (DM group) vs 13.81 ± 3.71 pmol/dL (non-DM group), there was no significant difference between the two for values of thyroid hormones.

Table 1: Demographic, thyroid and diabetic characteristics of the participants

	DM <i>n</i> = 100	Non-DM <i>n</i> = 100	p-value
Age (years)	40.70±8.02	34.85±10.38	<0.001
Males	44	61	
Females	56	39	
Thyroid volume (mL)	19.16±4.52	14.91±2.95	<0.001
Thyroid nodules	64	29	<0.001
TSH (mU/L)	2.87±2.42	2.04±1.90	0.68
FT3 (nmol/L)	2.00±0.79	1.62±0.51	0.53
FT4 (pmol/L)	26.40±5.27	13.81±3.71	<0.001
RBS (mg/dL)	282.30±45.05	93.38±2.93	<0.001
HbA1c (%)	8.11±1.93	5.25±0.22	<0.001

*p-value was calculated as $p < 0.05$ level.

The outcome of the functional interpretation of the thyroid function tests as presented in Figure 1 indicates that 92 out of the 100 non-diabetic volunteers have normal thyroid function with 4 having subclinical hypothyroidism and the remaining 4 having subclinical hyperthyroidism. In the DM group however, 58 patients showed some form of thyroid

dysfunction. 19 DM patients had subclinical hypothyroidism, 15 patients had subclinical hyperthyroidism, 10 patients had primary hypothyroidism while primary hyperthyroidism was recorded in 14 DM patients.

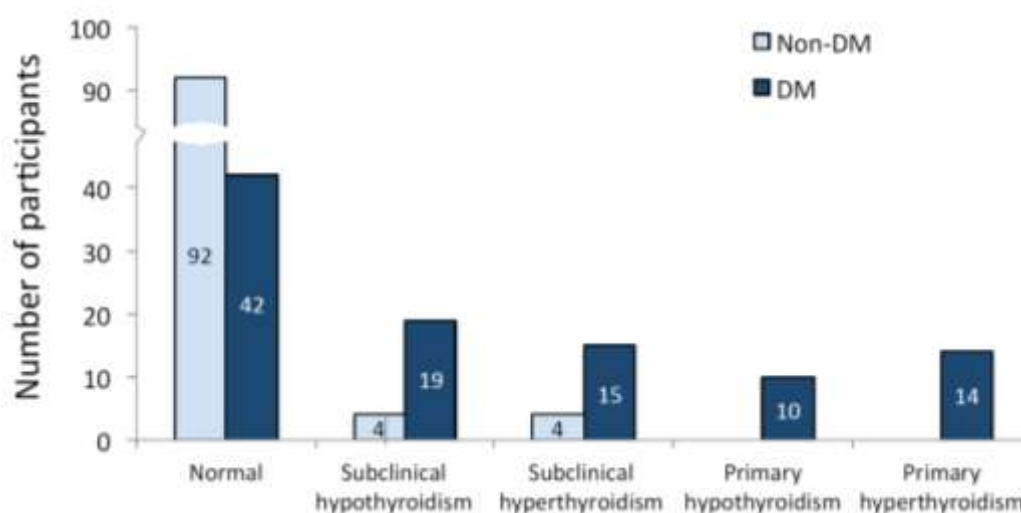


Figure 1: Frequency of the thyroid tests' functional interpretation between the DM and non-DM groups.

Only 8 out of the 100 non-DM participants had subclinical thyroid dysfunction whereas the DM group recorded 58 patients with thyroid dysfunction i.e. 19 subclinical hypothyroidisms, 15 subclinical hyperthyroidisms, 10 primary hypothyroidisms and 14 primary hyperthyroidisms.

To determine whether the thyroid volume and diabetic status of the patients were associated with the observed thyroid dysfunction, comparisons were made between the functional categories for values of thyroid volume, RBS and

HbA1c. This data is presented in Figure 2. Apart from patients with subclinical hyperthyroidism, the thyroid volume was significantly higher ($p < 0.05$) in patients with thyroid dysfunction compared to those with normal thyroid function. Patients with primary hypothyroidism and primary hyperthyroidism showed significantly higher ($p < 0.05$) levels of serum RBS compared to patients with normal thyroid function. All patients with thyroid dysfunction had significantly elevated HbA1c relative to those with healthy levels of thyroid hormones.

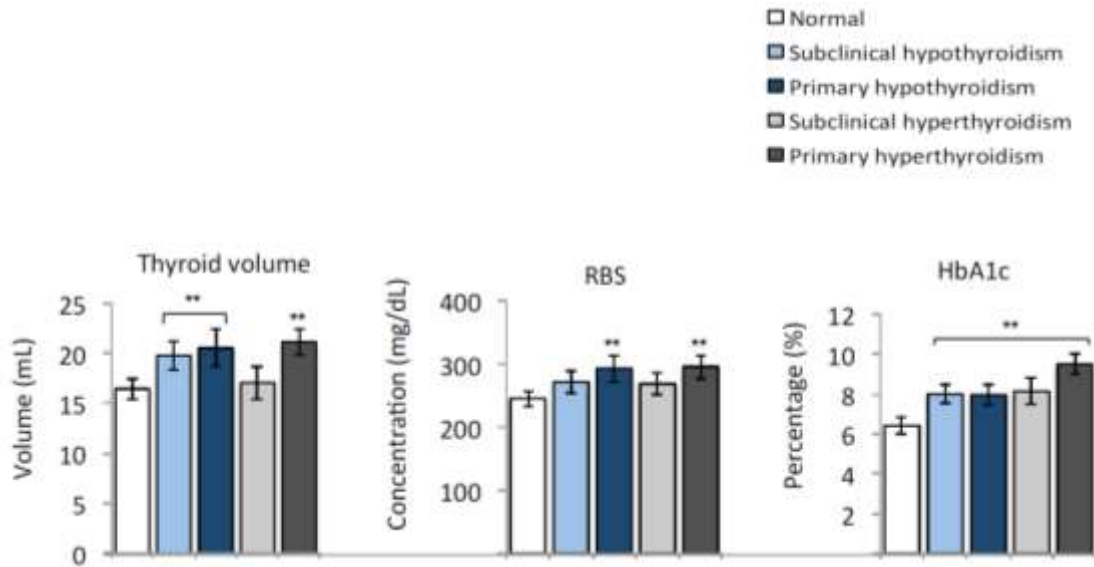


Figure 2: Categorized distribution of the different functional interpretation categories for values of thyroid volume, RBS and HbA1c in the DM group.

Thyroid volume was significantly higher in patients with thyroid dysfunction compared to those with normal thyroid function except subclinical hyperthyroidism. Patients with primary hypothyroidism and primary hyperthyroidism showed significantly higher levels of serum RBS compared to patients with normal thyroid function while all patients with thyroid dysfunction had significantly elevated HbA1c relative to those with healthy levels of thyroid hormones.

** signifies statistical significant difference compared to those with normal thyroid function at $p < 0.05$.

Pearson's correlation matrix (Table 2) revealed strong uphill correlation between thyroid volume and RBS ($r = 0.56$; $p = 0.001$) as well as HbA1c ($r = 0.56$; $p = 0.001$), while the presence of thyroid nodules showed moderate downhill correlation with thyroid volume ($r = -0.26$; $p = 0.001$), RBS ($r = -0.29$; $p = 0.001$) and HbA1c ($r = -0.24$; $p = 0.001$).

Table 2: Pearson's correlation matrix showing relationship between thyroid volume, RBS, HbA1c and presence of thyroid nodules

Variables	Thyroid volume	RBS	HbA1c	Thyroid nodule
Thyroid volume				
RBS	0.56**			
HbA1c	0.56**	0.89**		
Thyroid nodules	-0.26**	-0.29**	-0.24**	

** correlation is significant at the 0.01 level (2-tailed).

* correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

Our study analysed the comprehensive thyroid status of newly diagnosed type 2 DM patients with the findings recorded buttressing the relationship between thyroid dysfunction and onset of DM as reported by previous studies. This was first perceived from the high prevalence of thyroid nodules observed in the DM group of the present study as recent studies have suggested that the growth and development of thyroid nodules is related to insulin resistance and endogenous hyperinsulinemia in diabetic patients (35). Insulin resistance associated with type 2 DM have shown constant link with changes in thyroid morphology and hence affects the formation of nodules (36). Consequently, patients with pre-diabetes and diabetes have higher risk of developing thyroid nodules as well as increased thyroid volume (25).

It has been revealed that thyroid volume in type 2 DM forms as a result of chronic insulin resistance through stimulation of thyroid cell proliferation via the mitogen-activated protein kinase (MAPK) pathway (37). Nodularity of the thyroid could be suggestive of an existing metabolic dysfunction and can serve as an indicator of metabolic syndrome in otherwise non diabetic individuals as high prevalence of thyroid nodules have been reported in patients with metabolic syndrome with a positive correlation found between the degree of metabolic disorder and the occurrence of thyroid nodules (38).

Most noteworthy however, is the thyroid volume which is the widely used parameter for evaluation of pathological factors like iodine deficiency or multinodular goiter, thyroiditis, thyroid cancer, as well as the efficacy of levothyroxine therapy (39). Although variations in thyroid volume could be related to dietary iodine intake (40), ethnic

origin and anthropometric characteristics (41), prospective association with DM have been explored (42).

In type 1 DM, insulin resistance have been suggested to stimulate thyroid proliferation and as a result, changes in thyroid volume were observed (34). Subjects with type 2 DM-induced insulin resistance receiving metformin treatment have shown significant decrease in thyroid volume and thyroid nodule size (43). In this study, we reported significantly larger mean thyroid volume in DM patients compared to their non-DM counterparts ($p < 0.05$). Similarly, correlation analysis revealed strong relationship between thyroid volume and RBS as well as HbA1c. Patients with type 2 DM have a characteristic elevated HbA1c and studies have observed positive linear relationship between HbA1c and large thyroid volume or the presence of thyroid dysfunction (44), thus reassuring the need for routine thyroid volume check for type 2 DM patients.

To investigate the relationship between thyroid status and DM further, we conducted thyroid function tests and categorised the subjects based on functional interpretation of the tests. Our findings showed that more than 50% of the DM patients have some form of thyroid dysfunction with subclinical forms of hypothyroidism and hyperthyroidism having the highest prevalence. Sinha and Mukherjee have reported similar prevalence of subclinical hypothyroidism among diabetic patients (45) while Pramanik et al suggested that nearly all type 2 diabetes patients have subclinical forms of thyroid dysfunction in an eastern Indian population (46). Among patients with type 2 DM, subclinical hypothyroidism is the most prevalent form of thyroid dysfunction (7). Research have suggested that the chronic hyperglycemic condition of type DM triggers the onset of subclinical hypothyroidism. The prolong decline in assimilation of peripheral glucose leads to elevation of TSH secretion despite having normal thyroid hormones levels, thus by definition, subclinical hypothyroidism implies a raised serum TSH but a normal free T4 and T3(33).

The obvious relationship between thyroid dysfunction and increased thyroid volume was demonstrated by our findings as significantly larger thyroid was recorded in patients with primary hyperthyroidism, as well as subclinical and primary hypothyroidism compared to patients with normal hormone levels. Of particular interest however, is the effect of RBS and HbA1c on the different categories of functional interpretation. Our findings revealed that higher RBS levels could be associated with primary forms hyperthyroidism and hypothyroidism in type 2 DM patients. Interestingly, elevations in HbA1c was implicated in the development of all four (4) categories of abnormal thyroid hormone levels. Although RBS may provide an insight on the severity of DM (47), the HbA1c indicates the effect of chronic elevations in blood glucose level, making its assessment useful in monitoring diabetes management and therapy (48). Interestingly, studies have not only identified thyroid dysfunction in type 2 DM patients, but have been able to show that the dysfunction increase with elevations in HbA1c. These studies suggest that poor glycemic control may responsible for the development of thyroid dysfunction (44, 49). Since the present study focused on newly diagnosed type 2 DM patients, the observed elevations in HbA1c

among all categories of thyroid dysfunction indicates the strong influence chronic elevations in blood sugar levels have on thyroid function. Follow-up studies on these patients will reveal a more perspicuous association between HbA1c and thyroid dysfunction.

Therefore, our findings suggest that the development of thyroid dysfunction in type 2 DM patients may result from prolong elevated blood glucose levels and/ or the onset of insulin resistance which are characteristic of chronic diabetic condition.

It is important to indicate that the limitations of this study include exclusion of some factors that can affect thyroid function such as genetics, gender, age, anthropometric measurements from our analysis. Also, the relatively small sample size further narrowed the number of DM patients having thyroid dysfunction.

CONCLUSION

In conclusion, this study has provided experimental evidences that highlights the subsistence of thyroid dysfunction in type 2 DM - suggesting that the thyroid condition worsens with severity of the diabetic status. With large variations among different guidelines on assessment of thyroid dysfunction in newly diagnosed type 2 DM patients (with recommendations ranging from zero assessment to yearly intervals), this study hints that the prevalence and significance of thyroid dysfunction in type 2 DM is comparable to that of type 1 DM. Therefore, we recommend that baseline as well as routine assessment of thyroid status be conducted in type 2 DM patients.

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