

## دراسة اضطرابات الغدة الدرقية في المرضى المصابين بداء السكر من النوع الثانى الذين يترددون على مستشفى طرابلس المركزى

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### ملخص البحث :

داء السكرى من أكثر الأمراض شيوعاً فى العالم هذه الايام ، وأثبتت عدد من الدراسات ان اضطرابات الغدة الدرقية من الامراض الشائعة في البشر ، وداء السكرى واضطرابات الغدة الدرقية هما من أكثر أمراض الغدد الصماء شيوعاً خلال العمل الطبي السريري ، وتهدف هذه الدراسة لمعرفة مدى إنتشار اضطرابات الغدة الدرقية فى المرضى المصابين بداء السكر من النوع الثانى ، وهذه الدراسة هي دراسة مقطعية أجريت على عدد 200 مريض سكرى من النوع الثانى بمستشفى طرابلس المركزى -طرابلس بدولة ليبيا فى الفترة ما بين يوليو 2016 وحتى يوليو 2017 م وتتراوح اعمارهم بين 18 الى 70 سنة .

وقد تم تحليل عينات المرضى لهرمونات الغدة الدرقية FT3, FT4 and TSH وكذلك تم تحليل عينات المرضى للإجسام المضادة لهرمونات الغدة الدرقية Tg-Ab, AM-Ab and TR-Ab بواسطة جهازى توسو الاتوماتيكي ، وجهاز الإليزا ، وتم استخدم التحليل الإحصائي المتقدم باستخدام برنامج SPSS .

أظهرت النتائج ان نسبة إنتشار مرض الغدة الدرقية من جملة عدد 200 مريض بداء السكر المشاركين فى الدراسة بلغت 13.4 % منهم 2.9% مريض بانخفاض هرمون الغدة الدرقية ، 9 % تحت انخفاض هرمون الغدة الدرقية و1.5 % لديهم فرط فى نشاط هرمون الغدة الدرقية .

إن وجود الاجسام المضادة الذاتية بمرضى السكر من النوع الثانى ، تعتبر السبب الرئيسى فى انتشار وخطورة مرض اضطرابات الغدة الدرقية بمنطقة طرابلس – غرب ليبيا وخاصة عند النساء ، لذلك ينبغي لمرضى السكر من النوع الثانى إجراء

قحوصات روتينية دورية لمعرفة التشخيص المبكر والوقاية من المضاعفات الناتجة من هذا المرض .

## **The Study of Thyroid Dysfunction Among Diabetic Patients Type 2 patients Visiting Tripoli Central Hospital**

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### **Abstract**

Diabetes has become a big issue nowadays. Many studies have found that thyroid disorders are widely common with variable prevalence among the different populations. Thyroid diseases and diabetes mellitus are most common endocrine pathologies encountered in clinical practice. The main objective of the study is to assess the prevalence of thyroid dysfunction in patients with type 2 diabetes mellitus (type 2 DM) attending an outpatients Tripoli Central Hospital. This is a retrospective cohort study was carried out on 200 diabetic patient's type 2, of age from (18 – 70 years) in the period from July, 2016 to July, 2017. Data were collected using a structured interviewing questionnaire for thyroid dysfunction by testing thyroid profile FT3, FT4, TSH and thyroid Antibodies (Tg-Ab, AM-Ab and TR-Ab) using TOSOH, ELISA and enzymatic methods respectively.

Statistical analysis was performed using statistical package for social science (SPSS) version 21. Evaluation of patient's data was performed using the t-test results with P-value  $<0.05$  were considered statistically significant

There was a high evidence of thyroid disorders (13.4%) . The most common thyroid disorder found was subclinical hypothyroidism (9%) followed by hypothyroidism (2.9%) which was followed by hyperthyroidism (1.5%). Prevalence of thyroid disorders was found to be more in females as compared to males. Autoantibodies are the main causes of thyroid dysfunction, therefore, could be predict and increase risk of thyroid disease, especially in females. Periodic screening for Thyroid in all type2 diabetic patients is necessary.

**Keywords:** Diabetes, Autoantibodies , thyroid disorders, Libya

## 1- introduction

Diabetes mellitus (DM) is defined as a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly. The underlying cause of diabetes is the defective production or action of insulin, a hormone that controls glucose, fat, and amino acid metabolism.[1] Diabetes Mellitus (DM) and thyroid dysfunction (TD) are the two most common endocrine disorders in clinical practice [2]. The association between DM and TD is widely known, with the first studies published in 1979 [3]. Since then, several studies in different countries were conducted to estimate the prevalence of TD in diabetic patients. There is great variability in the prevalence of TD in general population, ranging from 6.6% to 13.4% [4,5]. In

diabetic patients, the prevalence is still greater and varies from 10 to 24% [5,6]. These differences can be explained by different diagnostic criteria of TD, the degree of iodine intake among different regions, different sensitivities of the TSH assays and the large population diversity [7]. Thyroid hormones play an indispensable role in various metabolic processes like carbohydrate metabolism, lipid metabolism and pancreatic function [8]. Alteration of thyroid hormones directly affects the basal metabolic rate. Patients with T2D commonly display the symptoms of hypothyroidism, and symptoms of hyperthyroidism have been documented in patients with type 1 diabetes [9,10]. Excess or deficiency of either insulin or thyroid hormones can result in functional abnormalities of one another, as both of them are closely involved in cellular metabolism. Some studies have suggested that diabetic patients with subclinical hypothyroidism are at risk of complications like nephropathy and cardiovascular events [11].

Thyroid disorders are very common in the general population and are second only to diabetes as the most common condition to affect the endocrine system. As a result, it is common for an individual to be affected by both thyroid diseases and diabetes. The first reports showing the association between diabetes and thyroid dysfunction were published in 1979. Since then, a number of studies in different countries have tried to estimate the prevalence of thyroid dysfunction among type 2 diabetic patients [12].

The diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult because poor glycaemic control can produce features similar to hyper-

thyroidism, such as weight loss despite increased appetite and fatigue. Severe diabetic nephropathy can be mistaken for hypothyroidism because patients with this condition may have edema, fatigue, pallor, and weight gain[13]. Therefore it is important to evaluate diabetic population regarding thyroid diseases clinically or subclinically, as one condition can worsen the other if left untreated in form of worsening of DM and dyslipidemias and causing diverse complications. Therefore, it is imperative to screen diabetic population regarding thyroid diseases[14]. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported [15]. It was observed that there was an increased frequency of thyroid dysfunction with advancing age and a higher prevalence of thyroid disease in women compared to men and in diabetic subjects compared to non-diabetic. Several reports documented a higher than normal prevalence of thyroid dysfunction in the diabetic population. Particularly, Perros et al. [16] demonstrated an overall prevalence of 13.4% of thyroid diseases in diabetics with the highest prevalence in type 1 female diabetics (31.4%) and lowest prevalence in type 2 male diabetics (6.9%). Recently, a prevalence of 12.3% was reported among Greek diabetic patients [17] and 16% of Saudi patients with type 2 diabetes were found to have thyroid dysfunction [18]. In Jordan, a study reported that thyroid dysfunction was present in 12.5% of type 2 diabetic patients [19]. Thyroid dysfunction in diabetes mellitus manifests either as hypothyroidism (clinical or subclinical) or hyperthyroidism (clinical or subclinical) and is reflected in the circulating levels of thyroid hormones, namely tri-iodothyronine

(T3), Thyroxine (T4) and thyroid stimulating hormone (TSH) which might have an impact on blood glucose homeostasis[2,3]. The aim of this paper is to investigate the prevalence of thyroid dysfunction FT3, FT4 and TSH levels in patients with type 2 diabetes through the data available in our diabetic centers among those who attended the diabetic clinics for routine checkup in Surman General hospital.

## **2.2 Amis of The Study**

### **2.2.1 General Objective:**

1. To assess the thyroid dysfunction among type 2 diabetic patients attending Tripoli Central Hospital.

### **2.2.2 Specific Objectives**

1. To measure the levels of thyroid hormone and fasting blood glucose level in type 2 diabetic patients attending Tripoli Central Hospital.
2. To compare the mean concentration of thyroid dysfunction among type 2 diabetic patients in study group.

## **3- Material and Methods**

### **3. 1 Study approach:**

This Study used quantitative research approach.

### **3. 2 Study Design:**

The design is cross sectional descriptive study.

### **3. 3 Study area:**

This study was done in Tripoli Central Hospital. Tripole, Libya.

**3. 4 Study period:**

This study was conducted in the period from July, 2016 to July, 2017.

**3. 5 Study population:**

This study was carried out on diabetic patient's type 2, samples were collected including both sex (110 males and 90 females) ranging of age from (18 – 70 years).

**3. 5. 1 Inclusion criteria:**

All diabetic patients type 2 attending Zawia Street General Hospital, were selected.

**3. 5. 2 Exclusion criteria:**

Non diabetic patients and those who have a sign and symptoms of clinical history other diseases were excluded.

**3. 6 Sample size:**

Three hundred and sixty nine samples were taken from diabetic patients type2 included in this study according to the following formula:

$$N = N (z)^2 p q / (n - 1) d^2 + (z)^2 p q$$

**3. 7 Ethical consideration:**

Approval to this study was obtained from Tripoli Central Hospital, Ministry of Health, Tripole, Libya. And verbal consent of patients was taken.

**3. 9 Data Collection and Analysis:**

Data were collected using a structured interviewing questionnaire. Statistical analysis was performed using statistical package for social science (SPSS) version 21. Evaluation of

patient's data was performed using the t-test results with P-value  $<0.05$  were considered statistically significant.

### **3.10 Sampling collection:**

5 ml of venous blood was collected ( 2 ml into fluoride oxalate for fasting blood glucose) and (3 ml into plain container, centrifuge to separate serum from the cells as soon as the clot was formed for thyroid function tests). Serum aliquots were stored at 4oC to be run in batches; tests were performed with Automated Immunoassay (TOSOH ST – AIA – Japan).

## **4. Methodology**

### **4.1 Method of fasting blood glucose:**

#### **Principle of the method:-**

Glucose in the sample originates, by means of the coupled reactions, a coloured complex that can be measured by spectrophotometer. Glucose reagent contains (substrate, standard) are provided ready for use.

#### **Procedure:**

### **4.2 Measurement of serum Free T3**

#### **Principle of T3 assay**

The ST AIA PACK FT3 is a competitive enzyme immunoassay which is performed entirely in the ST AIA –PACK iFT3 test cups. Free Triiodothyronine (FT3) present in the test sample competes with enzyme-labeled Triiodothyronine (T3) for a limited number of binding sites on a T3 –specific antibody immobilized on magnetic beads. The beads are washed to remove the unbound enzyme-labeled free triiodothyronine and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate(4MUP). The amount of enzyme-labeled free triiodothyronine that binds to the beads is inversely proportional



to the free triiodothyronine concentration in the test sample. A standard curve using a range of known standard concentration is constructed and unknown free Triiodothyronine concentration are calculated using this curve.

### 4.3 Calculation of the results

The TOSOH AIA System Analyzer perform all sample and reagent handling operations automatically. The TOSOH AIA System Analyzer read the rate of fluorescence produced by the reaction and automatically convert the rate to T3 concentration ng/ml.

Reference values of Free T3=2.17-3.34 pg/ml (3.34-5.14 pmol/l).

### 4.4 Measurement of serum Free T4

Principle of the assay

The ST AIA PACK FT4 is a competitive enzyme immunoassay which is performed entirely in the ST AIA –PACK FT4 test cups. The thyroxine not bound to serum proteins (free T4) competes with enzyme- labeled T4 for a limited number of binding sites on a T4 specific antibody immobilized on magnetic beads. After incubation the beads are washed to remove the unbound enzyme-labeled T4 and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled T4 that binds to the beads is inversely proportional to the free T4 concentrated in the test sample. A standard curve using a range of known standard concentrations is constructed and unknown sample free T4 concentration are calculated using this

curve. Reference Values of Free T4.= 0.82-1.63 ng/dl (10.6-21.0 pmol/l)

#### 4.5 Measurement of serum TSH

Principle of the assay

The ST AIA PACK TSH is a two – site immune enzymometric assay which is performed entirely in the ST AIA –PACK TSH test cups. TSH present in the test sample is bound with monoclonal antibody immobilized on magnetic beads and monoclonal antibody conjugated with bovine alkaline phosphatase in the test cups. The magnetic beads are washed to remove unbound enzyme – labeled monoclonal antibody and are then incubated with a fluorogenic substrate , 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme conjugated with monoclonal antibody that binds to the beads is directly proportional to the TSH concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve. Reference values of TSH= 0.38 - 4.31  $\mu$ IU / ml (0.38 – 4.31 mIU / l).

#### 5. Results and discussion

The study included 200 T2D patients in which the sex and age distribution of diabetic and non diabetic patients is shown in table 1. Type 2 DM patients include 110 males and 90 females.

**Table 1: General characteristics of study population**

Parameters		Frequency	Percent (%)
<b>Gender</b>	Male	110	55.0
	Female	90	45.0
	<b>Total</b>	<b>200</b>	<b>100.0</b>
<b>Residence</b>	Urban	178	88.9
	Rural	22	11.1
	<b>Total</b>	<b>200</b>	<b>100.0</b>
<b>Education Level</b>	Illiterate	12	6.2
	Tertiary	137	68.3
	Primary	23	11.4
	Secondary	28	14.1
	<b>Total</b>	<b>200</b>	<b>100.0</b>

Thyroid disease is a medical condition that affects the function of the thyroid gland, percentage and classification of history of thyroid gland is showing in figure 1. A family history of autoimmune thyroid disease is found in 3 percent of patients. Family history of thyroid disorder and dyslipidaemia was not significant. The obtained results shows that 13.4 % of the patients have thyroid disorders. The most common thyroid disorder found was subclinical hypothyroidism (9%) followed by hypothyroidism (2.9%) which was followed by hyperthyroidism (1.5%), this is clear in figure 3.

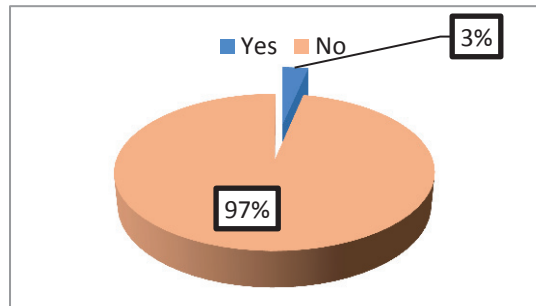


Figure 1 : Percentage and classification of History Of Thyroid gland

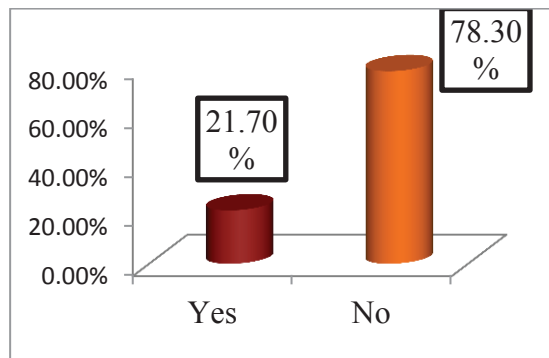


Figure 2: Percentage and classification of Obesity

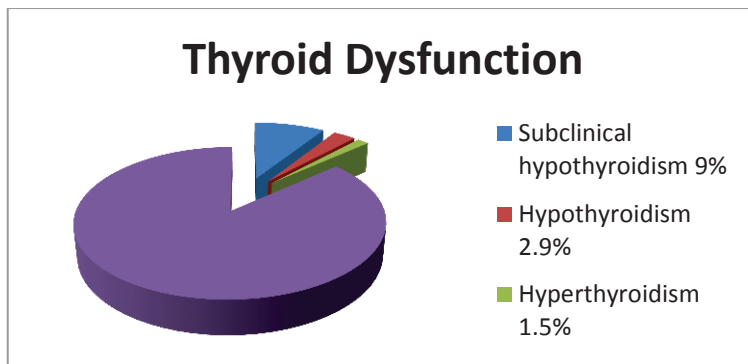


Figure 3: Shows percentage and classification of thyroid dysfunction among type2 diabetes mellitus patients.

**Table 2: Represents type of thyroid hormone disorders according to gender and auto-antibodies against (Thyroglobulin , Microsomal, TSH receptor) among the DM-type2 patients.**

Thyroid diagnosis	ATG-Abs	AM-Abs	TSH-Abs
<b>Euthyroid male 109</b>	-	-	-
<b>Female 72</b>	-	-	-
<b>Hypothyroid male 0</b>	0	0	0
<b>Female 4</b>	7	7	0
<b>Sub-clinical hypo male 1</b>	-	-	-
<b>female 11</b>	-	-	-
<b>Hyperthyroid male 0</b>	-	-	0
<b>Female 3</b>	-	-	5
<b>Total 200</b>	7	7	5

Table 2 shows that the Prevalence of thyroid disorders was found to be more in females as compared to males whereas table 3 illustrated that hyperthyroidism and subclinical hypothyroidism were the most prevalent disorder in diabetic patients in our study with lower FT3 ( $1.63 \pm 0.43$ ,  $2.91 \pm 0.28$ ) and FT4 ( $0.49 \pm 0.24$ ,  $0.90 \pm 0.12$ ) where as FT3 and FT4 in euthyroidism are  $2.71 \pm 0.32$ ,  $1.6 \pm 0.27$  respectively.

The level of serum thyroid hormones in diabetic shown in table 4 and 5. The serum levels of FT3, FT4 and TSH were significantly high in female patients ( $2.65 \pm 0.17$ ,  $1.51 \pm 0.30$  and  $2.48 \pm 0.31$ ) compared to male patients ( $2.19 \pm 0.23$ ,  $1.25 \pm 0.37$  and  $1.49 \pm 0.82$ ).

**Table 3: FBG and thyroid hormones (FT3, FT4 and TSH) levels in diabetic patients participants in the study (no=200) :**

Parameters	Laboratory Parameters			
DIAGNOSIS	FBG 70 -110 mg/dl	FT3 2.2– 3.3pg/ml	FT4 .8- 1.63ng/dl	TSH ,3- 4.3μIU/ml.
Euthyroidism 181	199.6±68.5	2.71±.32	1.6 ±.27	2.32 ±0.32
Clinical hypothyroidism 4	179.82±25.5	1.63 ±0.43	0.49 ±0.24	6.94 ±3.5
Sub-hypothyroid 12	164.5±45.6	2.91±.28	.90±.12	4.45±.32
Hyperthyroidism 3	201.1±19.5	7.23 (±0.13)	8.93 ±6.79	.10 ±0.02

**Table 4: Gender Wise Comparison of thyroid hormones mean Levels in Study Participants**

Parameters	Males Mean(±SD)	Females Mean(±SD)	<i>P-values</i>
<b>FT3</b>	2.19±0.23	2.65±0.17	0.043
<b>FT4</b>	1.25±0.37	1.51±0.30	0.134
<b>TSH</b>	1.49±0.82	2.48±0.31	0.001

**Table 5: The relationship between FBG and thyroid hormones**

Parameters	R-value	P-value
FT3	-0.025	0.939
FT4	-0.049	0.880
TSH	0.434	0.159

In our study it is clear that thyroid disorders are widely common with variable prevalence among the different populations. In the present study, the prevalence of thyroid dysfunction was 13.4%. The reported prevalence of thyroid dysfunction in diabetes varying from 2.2 to 17% [20]. Another study reported high prevalence of abnormal TSH concentration in patients with type 2 diabetes (T2D) (31%) [20]. In addition, diabetic women are more frequently affected than men and hypothyroidism is more common than thyrotoxicosis. Similarity of several studies reported, thyroiditis is most common disorders in type 2 DM patients with hypothyroidism[21].

Many researches carried out shows different rates from different parts of the world. For example in Spain was 32.4% while in Argentina was 48%. Data from the Wickham survey conducted in the late 1970s in the north of England revealed a prevalence of 6.6% of thyroid dysfunction in the adult general population [22]. In the Colorado Thyroid Disease Prevalence study involving 25,862 participants attending a state health fair, 9.5% of the studied population were found to have an elevated TSH, while 2.2% had a low TSH [23]. Altered thyroid hormones have been described in patients with diabetes especially those with poor glycaemic control. In diabetic patients, the nocturnal TSH peak is blunted or abolished, and the TSH

response to TRH is impaired[24]. Reduced T3 levels have been observed in uncontrolled diabetic patients. This “low T3 state” could be explained by an impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycaemic control. However, in a study by Coiro et al. involving type 1 diabetes patients with absent residual pancreatic beta cell function, an amelioration in glycaemic control did not restore.

The most effected thyroid dysfunction in this resarch was subclinical hypothyroidism, presented in 9% of patients with T2D. In Jordan, the overall prevalence of thyroid disease in T2D was 12.5% and the most common was subclinical hypothyroidism.[25]. The prevalence of undiagnosed thyroid disease in diabetic patients receiving community diabetes care was 5.5% (9.5% of female patients), and the prevalence of thyroid disease in the entire population of diabetic patients registered in the general practice was 10.8%. These findings suggest that screening for thyroid disease should be considered in patients receiving diabetes care in the community [26]. Among a diabetic clinic population of 5,000 there were 113 patients (1.1%) with concurrent clinical thyroid dysfunction (56 hyperthyroid, 57 hypothyroid). Seventy-one (62.8%) of these patients were insulin-dependent and diabetes preceded thyroid disease in 85 (75.2%). The value of screening diabetic patients for evidence of thyroid dysfunction is important . The Wickham survey found that thyroid dysfunction affected 6.6% of adults. There is a recognized association between thyroid disease and diabetes mellitus. The prevalence rate for thyroid disease was found to be 6.6% in the general population and 10.8%in diabetic patients. A variety of thyroid abnormalities may co-exist and



interact with diabetes mellitus. The reported frequency of hyperthyroidism and hypothyroidism in patients with diabetes has varied from 3.2 % to 4.6 % and 0.7 % to 4.0 % respectively). High prevalence of hypothyroidism particular in those with uncontrolled diabetes has been reported in Iranian patients. The combination of diabetes mellitus and primary hypothyroidism is not as rare as generally believed. Nine hypothyroid patients were found among 530 diabetic's patients a prevalence of 1.7% [20].

## 6-Conclusion

This study concludes that, the assessment of thyroid diseases is common in DM Libyan patients. Furthermore, Autoantibodies are the main causes of thyroid dysfunction, therefore, could be predict and increase risk of thyroid disease, especially in females.

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