

Rising Thyroid Disorders Among Type 2 Diabetic Mellitus Patients: Case-Control Study

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Abstract

Aim: The objective of study to explore the association between thyroid dysfunction and Type 2 diabetes mellitus (T2DM) related to family history and co-morbid conditions.

Methods: This was a case and control study, 762 T2DM patients and 762 control study participants were enrolled, aged between 25 and 65 years. The study based on biochemistry parameters included: fasting blood glucose levels (FBG), glycosylated hemoglobin (HbA1c), serum cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), thyroid stimulating hormone (TSH), T3, and T4.

Results: There were statistically significant differences between T2DM patients and control subjects regarding BMI, physical activity, smoking, metabolic syndrome, hypertension, family history thyroid nodules, and number of sleeping hours. The study found statistically significant differences between T2DM and control subjects on calcium ($p=0.028$), magnesium ($p<0.001$), potassium ($p<0.001$), phosphorous ($p=0.038$), fasting blood glucose ($p<0.001$), HbA1c ($p<0.001$), LDL ($p=0.002$), albumin ($p<0.001$), bilirubin ($p=0.015$), triglyceride ($p<0.001$), SBP ($p=0.009$) and, DBP ($p=0.002$), TSH ($p<0.001$), T3 ($p<0.001$), and T4 ($p<0.001$). There were statistically significant differences between subjects with and those without thyroid nodules for calcium ($p<0.001$), magnesium ($p<0.001$), phosphorous ($p=0.022$), HDL ($p=0.050$), TSH ($p<0.001$), T3 ($p<0.001$), and T4 ($p<0.001$). Multivariable stepwise logistic regression analysis showed that TSH mIU/L (<0.001), HbA1c ($p<0.001$), family history of thyroid ($p<0.001$), Waist circumference, ($p<0.001$), SBP mmHg ($p=0.002$), [DBP mmHg ($p=0.003$), BMI ($p=0.006$), Serum Calcium level (mmol/L) ($p<0.001$), and family history of DM ($p=0.015$) were considered at higher risk as a predictors of thyroid among T2DM patients.

Conclusion: The study found a high prevalence of thyroid dysfunction in Turkish T2DM patients compared to the general population. This study suggests that obesity, HbA1c, the environment, and genetic susceptibility among T2DM, may increase the risk of thyroid disease and cancer.

Keywords: epidemiology, thyroid disorder, T2DM, metabolic syndrome, prevention

1. Introduction

Type 2 diabetes mellitus (T2DM) and thyroid dysfunction are both the main threats world wide and affect the health and economic of most developed and developing countries (Alberti et al., 2009; Bener et al., 2009). T2DM

very rapidly increasing the risk of coronary heart diseases (Al-Wazzan et al., 2010; Bener et al., 2014; Bener et al., 2016) and thyroid dysfunction in the long term (Akbar et al., 2006; Marrero, 2009; Papazafiropoulou et al., 2010; Ghazali & Abbiyesuku, 2010; Wang et al., 2015; Centeno Maxzud et al., 2016; Sarfo-Kantanka et al., 2017; Malaguarnera et al., 2017; Bener et al., 2018). Although, lifestyle factors, regular physical exercise, appropriate diet are main essential elements in the prevention of T2DM (Bener et al., 2016).

Thyroid disorders and diabetes are two most common endocrinological medical conditions seen in general clinical medical practice (Al-Wazzan et al., 2010). The concurrence of the two medical conditions in the same individual can lead to achieving good glycemic control and prevent the cardiovascular risk associated with diabetes. (Alberti et al., 2009; Bener et al., 2009; Bener et al., 2016) Although, several studies have shown a higher prevalence of thyroid dysfunction occurs in T2DM patients and vice-versa (Akbar et al., 2006; Papazafiropoulou et al., 2010; Ghazali & Abbiyesuku, 2010; Wang et al., 2015; Malaguarnera et al., 2017).

T2DM is very common disease related to risk factor such as overweight, obesity, sedentary lifestyles, stress, hypertension, hyperglycemia, dyslipidemia (Bener et al., 2009; Bener et al., 2016; Marrero, 2009; Wang et al., 2015; Centeno Maxzud et al., 2016; Sarfo-Kantanka et al., 2017; Ghazali & Abbiyesuku, 2010). Several authors reported that T2DM as risk factor for coronary heart disease and thyroid thyroid nodules (Akbar et al., 2006; Marrero, 2009 ; Papazafiropoulou et al., 2010; Ghazali & Abbiyesuku, 2010; Wang et al., 2015; Centeno Maxzud et al., 2016; Sarfo-Kantanka et al., 2017; Malaguarnera et al., 2017). The range of thyroid disorders such as diabetes is very wide; and it is frequently does change in epidemiology, this has been observed by iodine levels seen in the population (Marrero, 2009; Weetman, 2011; Wang et al., 2015; Centeno Maxzud et al., 2016). In some parts of the world where intake of iodine, a major component of thyroid hormones which represent the most common cause of thyroid pathology (Sarfo-Kantanka et al., 2017).

The metabolic syndrome, obesity, and diabetes are considered major risk factors for thyroid dysfunction risk or thyroid cancer development (Leitzmann e al., 2010; Sarfo-Kantanka et al., 2011; Bener et al., 2018). The aim of this study was to explore the association between thyroid dysfunction and T2DM patients in relation to age, sex, lifestyle, obesity, family history and other co-morbid contributing risk factors.

2. Subjects and Methods

This study was designed as a case and control based on subjects age ranged between from 25 to 65 who visited the diabetes clinics, endocrinology clinics, thyroid surgery and outpatient clinics at the Istanbul University of Medipol, Medipol Hospital Groups from January 2016 to April 2018. This case and control study was based on 762 type 2 diabetic and 762 control subjects.

2.1 Laboratory Measurements

Case T2DM patients were considered according to American Diabetes Association (ADA 2014) and International Diabetes Federation (IDF) World Health Organization (WHO) (Alberti et al. 2009; Bener et al., 2009; Bener et al., 2014; ADA, 2014) (i.e (1) fasting venous plasma glucose concentration ≥ 7.0 mmol/l (2) 2-hour venous plasma glucose concentration ≥ 11.1 mmol/l; or (3) HbA1c ≥ 6.5 . Subjects reporting a history of DM and receiving antihyperglycemic therapy also were considered having diabetes mellitus. The inclusion criteria comprised of diagnosis of T2DM in conformity with international standards by ADA and IDF (Alberti et al., 2009; Bener et al., 2009; ADA, 2010).

A subject was included in the control group (subjects without diabetes) if FPG was less than 7.0mmol/L (126 mg/dL) and HbA1c less than 48 mmol/mol (6.5%) and no use of diabetes medications was reported.

2.2 Thyroid Evaluation

Thyroid function was evaluated by measuring thyroid stimulating hormone (Gharib et al., 2005) (TSH), T3, and T4, using immunochemoluminescent assays by an automated analyzer (Immulite, 2000; Diagnostic Products, Los Angeles, CA, USA). Also, thyroid fine needle aspiration biopsy was considered for patients if thyroid nodules were greater than 1.00 cm (Bener et al., 2018). Further, the study based socio-demographic characteristics, lifestyle habits and biochemical parameters, physical exercise and family history and co-morbid medical conditions.

The SPSS computer software for Windows, Version 22.0 was used to determine the significance of differences between mean values of two continuous variables. Chi-square and Fischer's exact tests were conducted for the differences between two or more categorical variables. Multivariate logistic regression analysis was used to assess the relationship between dependent and independent variables and to determine possible the risk factors for the existing of thyroid nodules among T2DM patients and p value less than 0.05 considered significant.

3. Results

Table 1 summarizes the study socio-demographic variables of T2DM patients and control subjects. As can be seen from this table most of variables BMI, physical activity, smoking, metabolic syndrome, hypertension, family history thyroid nodules, and number of sleeping hours appeared statistically significant differences between T2DM patients and control subjects.

Table 1. Socio-demographic and clinical characteristics of studied T2DM patients and control subjects (N=1,524)

	T2DM n = 762	Control n = 762	
Age groups (in years)			
<40	201(26.4)	207(27.2)	
40-49	177(23.2)	212(27.7)	0.100
50-59	168(22.0)	161(21.2)	
>60 and above	216(23.8)	182(23.9)	
Gender			
Male	312(40.9)	335(44.0)	0.233
Female	450(59.1)	427(56.0)	
BMI (kg/m ²)			
Normal (<25 kg/m ²)	213(28.0)	284(37.4)	0.001
Overweight (29-30 kg/m ²)	342(44.9)	342(45.0)	
Obese (>30 kg/m ²)	207(27.1)	134(17.6)	
Physical activity			
Yes	214(28.1)	202(28.1)	0.026
No	548(73.9)	560(73.5)	
Smoking status			
Never	634(83.2)	561(73.6)	0.001
Current smoker	85(11.2)	98(12.9)	
Past smoker	43(5.6)	103(13.5)	
Metabolic Syndrome ATP -III			
Yes	267(35.0)	76 (10.0)	0.001
No	495(65.0)	686 (90.0)	
Family history of hypertension			
Yes	151(19.8)	102(13.4)	0.001
No	611(80.2)	660(86.6)	
Family history of Thyroid nodule:			
Yes	108(14.2)	46(6.0)	0.001
No	654(85.8)	716(94.0)	
Number of Sleeping hours	5.90± 0.92	6.52±1.16	0.001
BMI kg/m ²	27.60± 4.54	26.50±6.39	0.001

Table 2 presents the biochemistry parameters value among value among T2DM and control subjects. The analysis revealed significant differences between T2DM and control subject for calcium (p=0.028), magnesium (p<0.001), potassium (p<0.001), phosphorous (p=0.038), fasting blood glucose (p<0.001), HbA1c (p<0.001), LDL (p=0.002),

albumin ($p<0.001$), bilirubin ($p=0.015$), triglyceride ($p<0.001$), SBP ($p=0.009$) and, DBP ($p=0.002$), TSH ($p<0.001$), T3 ($p<0.001$), and T4 ($p<0.001$). . Statistically significant differences were found between T2DM and control subject regarding.

Table 2. Clinical biochemistry baseline value among T2DM and control subjects (N=1,524)

Variables	T2DM	Control	P value
	N =762	N = 762	
	Mean \pm SD	Mean \pm SD	
Hemoglobin (g/dL)	12.85 \pm 2.32	13.04 \pm 2.46	0.285
Magnesium (mmol/L)	0.79 \pm 0.08	0.92 \pm 0.09	<0.001
Potassium (mmol/L)	3.72 \pm 0.91	4.46 \pm 0.76	<0.001
Calcium (mmol/L)	1.74 \pm 0.67	1.92 \pm 1.24	0.001
Phosphorous (mmol/L)	1.28 \pm 0.97	1.20 \pm 0.63	0.038
Creatinine(mmol/L)	65.59 \pm 16.90	63.83 \pm 12.22	0.101
Fasting Blood Glucose(mmol/L)	7.36 \pm 1.02	6.27 \pm 1.42	<0.001
HbA1c	7.58 \pm 1.47	6.02 \pm 1.32	<0.001
Cholesterol (mmol/L)	4.80 \pm 1.04	3.23 \pm 1.19	<0.001
HDL (mmol/L)	1.34 \pm 0.19	1.31 \pm 0.14	0.911
LDL (mmol/L)	1.91 \pm 0.50	2.11 \pm 0.94	0.002
Albumin (mmol/L)	40.67 \pm 9.22	36.84 \pm 10.18	<0.001
Billirubin (mmol/L)	9.19 \pm 5.25	9.84 \pm 4.18	0.015
Triglyceride (mmol/L)	1.96 \pm 1.03	1.23 \pm 0.70	<0.001
Uric Acid (mmol/L)	271.6 \pm 76.87	293.5 \pm 78.6	<0.001
Systolic Blood Pressure mm Hg	129.98 \pm 15.06	126.89 \pm 15.98	0.009
Diastolic Blood Pressure mm Hg	78.96 \pm 10.82	77.64 \pm 9.81	0.002
Thyroid stimulating hormone -TSH	2.70 \pm 1.00	1.95 \pm 1.13	<0.001
T3	1.86 \pm 1.01	1.21 \pm 0.71	<0.001
T4	1.21 \pm 0.71	0.88 \pm 0.31	<0.001

TSH (reference range, 0.35–4.0 mIU/l), free tri-iodothyronine (FT3; reference range, 1.71–4.71 pg/ml), and free thyroxine (FT4; reference range, 0.8–1.9 ng/dl).

The results of the Clinical biochemistry comparison for T2DM with thyroid and without thyroid nodules are presented in Table 3. As can be seen from this table, the results were statistically significant differences for calcium ($p<0.001$), magnesium ($p<0.001$), phosphorous ($p=0.022$), HDL ($p=0.050$), TSH ($p<0.001$), T3 ($p<0.001$), and T4 ($p<0.001$) between subjects with and those without thyroid nodules.

Table 3. Clinical biochemistry baseline value among T2DM with thyroid nodules and without thyroid nodules

Variables	T2DM With thyroid nodule N=192 Mean ± SD	T2DM Without thyroid nodule N = 570 Mean ± SD	P value
Hemoglobin (g/dL)	12.80± 2.35	13.01±2.48	0.246
Magnesium (mmol/L)	0.76±0.10	0.92±0.11	<0.001
Potassium (mmol/L)	3.48±0.36	3.80±0.25	0.462
Serum Calcium level (mmol/L)	1.55±0.44	1.81±0.72	<0.001
Phosphorous (mmol/L)	1.41±0.30	1.43±0.65	0.022
Creatinine(mmol/L)	65.21±15.34	65.71±17.42	0.824
Fasting Blood Glucose(mmol/L)	7.33±0.91	7.59±1.00	0.694
HbA1c	7.49±0.97	7.28±1.08	0.008
Cholesterol (mmol/L)	4.79±1.00	4.80±1.05	0.969
HDL (mmol/L)	1.94±0.73	1.13±0.36	0.001
LDL (mmol/L)	1.91±0.76	1.58±1.00	0.045
Albumin (mmol/L)	40.1±9.55	40.8±7.50	0.376
Billirubin (mmol/L)	9.63±3.62	9.02±3.58	0.253
Triglyceride (mmol/L)	1.93±0.94	1.97±0.79	0.736
Uric Acid (mmol/L)	271.8±70.3	270.4±79.0	0.844
Systolic Blood Pressure mm Hg	130.6±15.6	127.9±15.4	0.036
Diastolic Blood Pressure mm Hg	79.4±9.4	77.8±9.6	0.045
Thyroid stimulating hormone -TSH	2.91±0.86	2.63±0.99	<0.001
T3	2.19±0.97	1.75±1.12	<0.001
T4	1.50±1.02	1.10±0.55	<0.001

The results of multiple logistic regression analysis are shown in Table 4. TSH mIU/L [OR 3.35 95% CI 1.73-5.98, <0.001], HbA1c [OR 2.95 95% CI 1.73-4.74, p< 0.001], family history of thyroid [OR 2.83 \ 95% CI 1.65-4.57, p= 0.001], Waist circumference, cm [OR 2.62 95% CI 1.89-3.53, <0.001], SBP mmHg [OR 1.45 95% CI 1.18-1.85, p= 0.002], [DBP mmHg [1.57 95% CI 1.24-1.99, p= 0.003], BMI [OR 2.55 95% CI 1.76-4.43, p= 0.006], Serum Calcium level (mmol/L) OR 2.12 95% CI 1.10-3.66, p=0.009], and family history of DM [OR 1.81 95% CI 1.22-2.64, p= 0.015] were considered at higher risk as a predictors of thyroid among T2DM patients.

Table 4. Multivariate logistic regression analysis for predictors presence of thyroid disorder among T2DM patients

Independent Variables	Odds Ratio	95% Confidence Interval	P Value
TSH, mIU/L	3.35	1.73-5.98	<0.001
HbA1C	2.95	1.73-4.74	<0.001
Family history of thyroid	2.83	1.65-4.57	<0.001
Waist circumference, cm	2.62	1.89-3.53	<0.001
Systolic blood pressure, mmHg	1.45	1.18-1.85	0.002
Diastolic blood pressure, mmHg	1.57	1.24-1.99	0.003
BMI (kg/m ²)	2.55	1.76-4.43	0.006
Serum Calcium level (mmol/L)	2.12	1.10-3.66	0.009
Family history of DM	1.81	1.22-2.64	0.015

4. Discussion

There are few studies comparing the prevalence of T2DM with thyroid dysfunction patients and controls subject as worldwide. Our study has revealed a higher rate of thyroid nodules in T2DM subjects compared to control subjects. The finding of this study is consistent with those based in Kuwait Al-Wazzan et al. (2010), Greece (Papazafiropoulou et al., 2010), Saudi Arabia (Akbar et al., 2006), Nigeria (Ghazali et al., 2010), Ghana (Sarfo-Kantanka et al., 2010) and Jordan (Radaideh et al., 2004) who recorded significantly higher prevalence of thyroid nodules in T2DM subjects compared to controls, with prevalence ranging between 10% and 40% among T2DM subjects (Chen et al., 2010). However, these large variations could be based on different diagnostic criteria of dysfunction, geographical locations, different sensitivities of the TSH assays and the large population diversity (Chen et al., 2010; Palma et al., 2013).

Also, T2DM is considered as risk factor and complication concerning thyroid. It is worth to note that very impress prevention of T2DM is necessary to reduce the increases rate of thyroid in the population. Further, the current subjects with T2DM also had a higher prevalence and larger thyroid nodules size which is confirmative with an earlier reported strong correlations between insulin resistance and thyroid nodule size (Al-Wazzan et al., 2010; Sarfo-Kantanka et al., 2017).

In fact, T2DM and thyroid dysfunction are highly correlated as the two commonest endocrinological medical conditions reported in clinical practice (Akbar et al., 2006; Marrero, 2009; Papazafiropoulou et al., 2010; Ghazali & Abbiyesuku, 2010; Wang et al., 2015; Centeno Maxzud et al., 2016; Sarfo-Kantanka et al., 2017; Malaguarnera et al., 2017). Further, some authors indicated that thyroid volume are associated with iodine deficiency and supply, Body Mass Index, gender, age, cigarettes smoking, genetic factors, FBG and T2DM severity (Bener et al., 2009; Duran et al., 2014; Kir et al., 2018; Rezzonico et al., 2008; Bener et al., 2018). The current study is consistent with earlier reported the correlation between metabolic disorders characterized by insulin resistance and the risk of thyroid cancer (Marrero, 2010; Ghazali et al., 2010; Chen et al., 2010; Kir et al., 2018; Bener et al., 2018).

Furthermore, increases thyroid cancer risk in diabetics might be related to several factors including, abnormal HbA1C and metabolic syndrome, triglyceride levels, obesity, dietary, and lifestyle (Marrero, 2010; Aschebrook-Kilfoy et al., 2011; Bener et al., 2018). Obese subjects were at ten times more risk of developing diabetes (Aschebrook-Kilfoy et al., 2011), and obesity was correlated with an increased risk of thyroid cancer (Leitzmann et al., 2010). Our sample demonstrated significant prevalence of thyroid dysfunction among T2DM compared to controls.

5. Conclusion

The study found very high rate of thyroid dysfunction in Turkish T2DM patients compared to the general population. This study suggests that obesity, HbA1c, the environment, and genetic susceptibility among T2DM, may increase the risk of thyroid dysfunction and cancer. The high prevalence of thyroid dysfunction among T2DM which may require routinely screening for thyroid disease.

Key Messages

1. There is a strong positive associations between the T2DM and thyroid dysfunction population.
2. This study reveals that an increase in thyroid dysfunction might be caused by increases in Metabolic Syndrome, HbA1C, diabetes and obesity.

Contributors

AB, MÖ and YÖ designed and supervised the study and were involved in data collection, statistical analysis and the writing of the paper. AOAA, CCB were involved in study designed, interpretation of data and writing of the manuscript. All authors approved the final version.

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Conflict of Interest

No conflict of interest was declared by the authors.

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