ACTA MEDICA SALINIANA

ORIGINAL PAPERS

DIABETES AND AUTOIMUN THYROID DISEASE THROUGH THE PRISM OF SOME METABOLIC ABNORMALITIES

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ABSTRACT

Introduction: Thyroid dysfunction (TD) and diabetes mellitus (DM) are the two most common chronic endocrine disorders with variable prevalence among different populations. Both insulin and thyroid hormones are linked by autoimmunity and are an important part of the metabolic syndrome. However, the correlations between T2DM and TD have not yet been sufficiently defined, followed by ambivalent results from previous studies.

Objectives: The study was conducted to compare the metabolic parameters of patients with T2DM with and those without AITD so as to determine the existence of a correlation between these and hormonal parameters (TSH, FT4).

Design and methods: This are documented observational case-control study that included 31 subjects with T2DM and AITD and 25 with T2DM without AITD. Sessions were conducted at the Clinic for Internal Medicine of the University Clinical Center in Tuzla. Individual metabolic parameters were analyzed, and in a broad evaluation, the values of hormonal and immune parameters were monitored and documented.

Results: There were no differences in age, gender and BMI of the examined groups. There was a statistically significant difference between the values related to OS, SKT, DKT, PGN, 2h ppPG, and HbA1c. A statistically significant correlation was found between TSH and females, FT4 and BMI (rS = 0.375 p value = 0.045) as well as a correlation between TSH and HbA1c (rS = 0.313 p value = 0.019) and TSH and 2x ppPG (rS = 0.281, p value = 0.036).

Conclusion: The expression of metabolic control parameters is strongest in the group of patients with diabetes and AITD. Their identification as a risk factor and the detection of their subclinical signs are extremely important for the early implementation of preventive and therapeutic strategies, which could change the course of diabetic complications and significantly improve prognosis of diabetes.

Key words: *diabetes mellitus, autoimmune thyroid disease, metabolic syndrome, TSH, BMI.*

INTRODUCTION

The incidence of TD among patients with DM 2 type (T2DM) ranges from 9.9% to 48% [1].

The NHANES III study reported a higher prevalence of TD in subjects in the United States with diabetes compared with those without diabetes, particularly among patients with positive antibodies to thyroid peroxidase (TPOAb) [2].

The relationship between T2DM and TD is not yet well determined. There are significant reports of higher TSH levels among patients with MetS than among the healthy ones, as well as a high prevalence of MetS over subjects with TSH levels higher than normal [3]. Whether a change in weight led to a TD or vice versa is yet controversial. Hypothyroidism is associated with a higher body mass index (BMI) and a higher prevalence of obesity [4]. Obesity itself can promote insulin resistance and diabetes, because adipose tissue is an active endocrine tissue that releases fatty acids, leptin, adiponectin, resistyn and others that are playing an important role in glucose and lipid metabolism [5]. The current Clinical Guideline of the European Society of Endocrinology recognizes the high prevalence of hypothyroidism in obesity and recommends a review of thyroid function for all the obese patients [6].

Hypo and hyperthyroidism deteriorate glycemic control in patients with diabetes. TD may exacerbate subclinical DM and increase the risk of diabetic complications in patients with T2DM. Conversely, poor glycemic control among

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older women with T2DM has also been associated with an increased risk of hypothyroidism that can cause insulin resistance [7].

Given the clinical implications of the coexistence of DM and TD, a systemic approach to thyroid testing in DM is highly required. Although for patients with T1DM, international guidelines recommend thyroid screening at the beginning of diagnosis and once a year thereafter, there are no specific recommendations for T2DM [8].

RESPONDENTS, STUDY DESIGN AND RESEARCH METHODS

The research was conducted as an open case-control study. The study sample consisted of 56 patients divided into 2 groups.

Subjects: Patients with T2DM and AITD (n = 31)

Control: Patients with T2DM without AITD (n = 25)

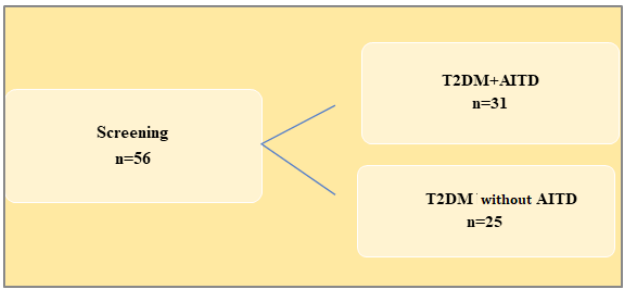

Figure 1. Study design with stratification of respondents by groups.

Data on a patient with diabetes include information related to date of birth, sex, duration of diabetes and AITD, history of medication, family history.

Anthropometric and clinical parameters include: body weight (kg), body height (cm), body mass index (BMI kg / m2), waist circumference (OS in cm), blood pressure (mmHg).

Biochemical variables include glycemic control parameters (PGN-fasting plasma glucosa, ppPG-postprandial plasma glucose, HbA1c-glicosilated hemoglobin).

Hormonal parameters include: thyroid hormone values (FT_4, TSH).

Immunological parameters include: values of antibodies to thyroid peroxidase (antiTPO).

Working definitions of clinical entities

Autoimmunity thyreoid disease (AITD) is defined as an antiTPO level greater than 60 IU / ml.

Hypothyroidism is defined where the T_4 levels are low with elevated TSH levels, i.e. the study included patients who had hypothyroidism as a diagnosis of discharge, laboratory results of thyroid stimulating hormone (TSH) and free thyroxine (T_4) indicative of hypothyroidism.

Hyperthyroidism involves low TSH and elevated FT_4.

Euthyroid patients are defined as individuals who have normal T_4 and TSH. The American Thyroid Association recommends the combined use of TSH and FT_4 as the most effective combination of blood tests to diagnose and monitor both outpatient and inpatient subjects.

Diabetes mellitus is defined as a diagnosis of diabetes reported in the medical history or fasting blood glucose level ≥7 mmol / L and postprandial blood glucose ≥11.1 mmol.

The examination was approved by the ethics committee, and the information was taken from everyone.

Statistical data processing

Statistical analysis was performed with the application program IBM SPSS Statistics 25 (IBM Corp. Released in 2017). IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Standard methods of descriptive statistics were used in data processing. Among the methods of analytical statistics, Student's T test and one-factor numerical analysis of variance (ANOVA) were used, as well as the sum of ranks test and Kruskal-Walliss analysis of variance (for nonparametric data). Due to the asymmetry of the groups, additional testing of the normality of the distribution of the results of the dependent variables for these two groups of subjects was performed using the Kolmogorov and Smirnov test. These results were further confirmed with the Shapiro-Wilk test. Speerman correlation coefficients and linear regression analysis were calculated to assess any significant association between MetS components and thyroid profile parameters (TSH and FT_4 levels). $P < 0.05$ was taken as a statistically significant.

RESULTS

The study included a total of 56 respondents divided into two groups. The first group consisted of 31 subjects with T2DM and AITD, and the second group consists of 25 patients with T2DM without AITD

The study was dominated by women patients. There was a total of 21.42% (n = 12) men and 78.57% (n = 44) women. The study was dominated by women, with a total of 21.42% (n = 12) men and 78.57% (n = 44) women. In the T2DM group with and without AITD, most patients had a positive family history of diabetes (93.5% vs. 84%). The incidence of hypothyroidism (71%) as coexisting AITD was highest compared to other thyroid dysfunctions. All patients with hypothyroidism were on levothyroxine substitute therapy.

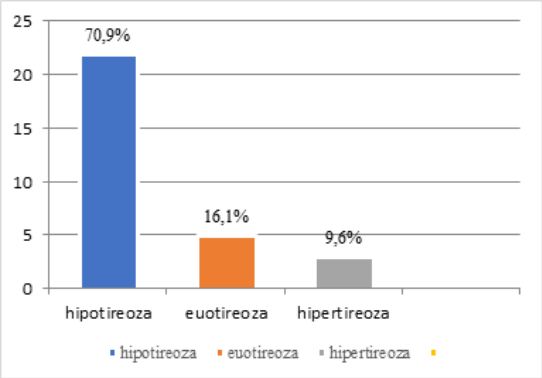

Figure 2. Distribution of AITD among T2DM.

Table 1. Mean values of TSH, FT4, antiTPO in groups with and without AITD.

PARAMETERS	T2DM with AITD n=31	T2DM without AITD n=25
FT4	13,7±4,22	15,88±3,2
TSH	11,16±14,91	1,98±0,73
antiTPO	1130,55±973,09	25,44±14,69

Legend: the parameters are expressed as mean, and the average deviation from the mean.

Duration of AITD

The median duration of AITD in T2DM is 5.87 +/- 1.4 years (Figure 3). In all our subjects, AITD was diagnosed after diabetes

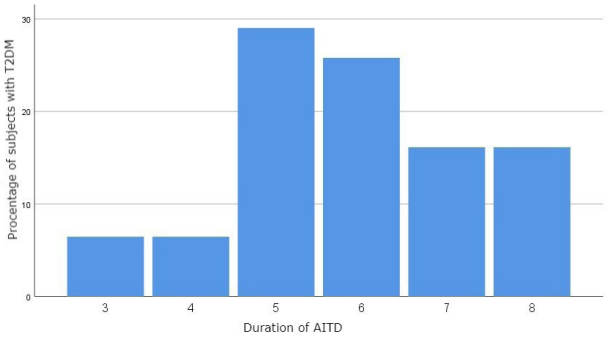

Figure 3. Duration of AITD in subjects with T2DM. Examination of the normality of the distribution using the Kolmogorov-Smirnov test with the level of statistical significance, p <0.05.

These results were further confirmed with the Shapiro-Wilk test.

Table 2. Comparing basal values of anthropometric and clinical parameters of subjects with T2DM and AITD and control groups (T2DM without AITD).

Parameters		T2DM with AITD (n=31)	T2DM without AITD (n=25)	P- value ◊
Age		58,7±18	59,8±13	0,864▲
Interviewee gender				
	M	7 (22,6%)	5 (20%)	0,819▲
	F	24 (77,4%)	20 (80%)	
Family history of the respondents	Positive	29 (93,5%)	21 (84%)	0,259▲
	Negative	2 (6,5%)	4 (16%)	
Duration T2DM		8,52±1,98	7,2±1,97	0,010
BMI in kg/m²		33,74±4,45	31,8±5,09	0,242▲
Waist circumference in cm		101,65±13,05	92,48±11,48	0,006
SKT (mmHG)		143,71±12,76	128,4±10,67	0,002
DKT (mmHG)		86,61±7,3	80,±4,54	0,001
PGN (mmol/L)		10,22±1,88	8,3±1,91	
ppPG (mmo/L)		13,1±2,38	10,3±2,6	
HbA1c (%)		11,28±2,12	8,72±1,68	

Legend: parameters are expressed as mean, mean deviation (SD), percentage value (%); BMI- Body Mass Index; SKT - systolic blood pressure; DKT - diastolic blood pressure; PGN- plasma fasting glucose; ppPG-postprandial plasma glucose; HbA1c- glycosylated hemoglobin; ◊ = T-test of independent samples; p <0.05; ▲ - no significance (NS).

The results of the T-test of independent samples showed significant differences in systolic blood pressure (143.71 vs, 128.40; p = 0.000), diastolic blood pressure (86, 61 vs, 80.4; p = 0.000), waist circumference. 101.65 vs, 92.48; p = 0.006), disease duration (8.52 vs, 7.2; p = 0.010), with mean values being significantly higher in the group of patients with T2DM and AITD compared to control. There were no significant differences in age, positive family history, body mass index. Glucose parameters in the group of patients with T2DM and AITD show significantly lower glycemic control compared to the control group (p <0.05).

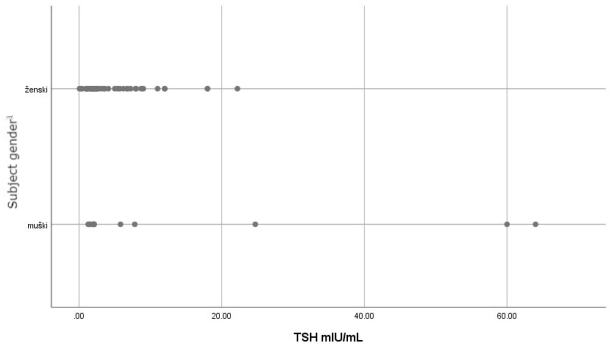

Figure 4. The figure shows the relationship between gender and TSH of the subjects with T2DM and AITD. A statisticaly significant association between TSH and female sex was determined by linear regression.

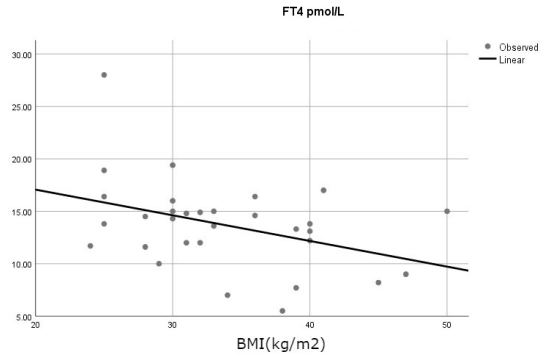

Figure 5. The figure shows Speerman's correlation of BMI and FT4 subjects with T2DM and AITD. It was found that there is a statistically significant negative correlation between FT4 height and BMI. (rS = 0.375 p value = 0.045).

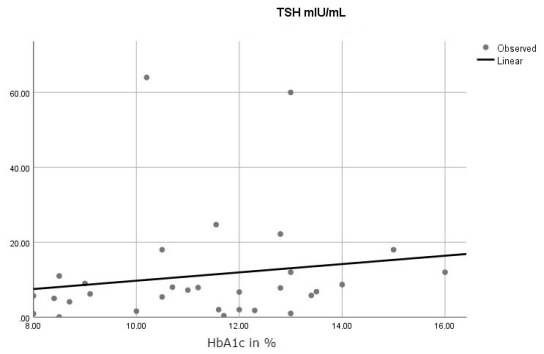

Figure 6. The figure shows the Speerman correlation of TSH and HbA1c subjects with T2DM and AITD. It was found that there is a statistically significant positive correlation between TSH height and HbA1c. (rS = 0.313 p value = 0.019).

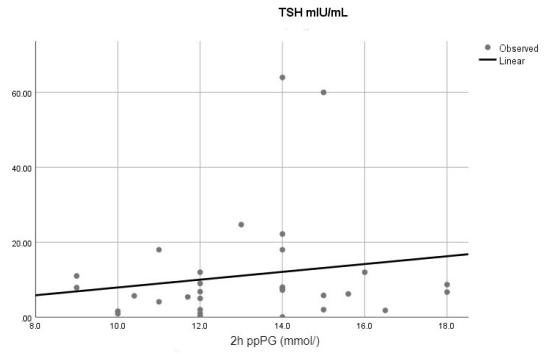

Figure 7. The figure shows the Speerman correlation of TSH and SHUK ppPG of T2DM subjects with AITD. It was found that there is a statistically significant positive correlation between TSH height and SHUK ppPG (rS = 0.28 p value = 0.036).

DISCUSSION

Many studies report higher levels of thyroid-stimulating hormone (TSH) in patients with metabolic syndrome than in healthy people, and a high prevalence of metabolic syndrome in subjects with TSH levels higher than normal. [3]. However, the association between thyroid dysfunction and metabolic syndrome components is still debatable [9]. In our study, hypothyroidism predominates over other thyroid dysfunctions. The cause of thyroid dysfunction in our study is autoimmune thyroid disease. Although the earlier causes of hypothyroidism are related to iodine deficiency, the situation has changed in recent decades. Hypothyroidism is now the most common cause of chronic autoimmune thyroid disease, with a consequent increase in TSH levels [10]. Our results agree with mentioned above, and are identical to the study from Greece, which also has the highest prevalence of autoimmune hypothyroidism in patients with T2DM [11]. The reason for the high prevalence of hypothyroidism in our study is that these are mostly previously known cases of overt hypothyroidism on substitution therapy.

Our study included patients with T2DM with an AITD with a mean age of 58.7 years and without AITD with a mean age of 59.81 years. Research has shown that the prevalence of T2DM increases with age, which corresponds to most studies [12], and autoimmune thyroiditis is also characterized by increased age-related prevalence. This is in line with a pattern published by Chinenye et al. in a multicenter study involving patients with diabetes [13].

Similar to ours, Ofoegbu and co-workers report an average age of 59.2 years in the Enguu study [14]. In our study in patients with T2DM and AITD, the majority of study participants were women, as well as in the control group. It is similar to a study conducted by Meng et al. [15] where women had a higher incidence of thyroid dysfunction than men, as well as to studies by Ranabir et al. [12]. However, in the group of respondents, a significant influence of the females on TSH was found. Hashimoto's thyroiditis is 5-10 times more common in women than in men [16]. From the above, we see that female dominance in our study is similar to that of 60.5% reported by the Diabcare Nigeria study group in 2012 [17]. Thus, we can conclude from the above that the prevalence of thyroid disorders in T2DM is influenced by the female sex. Obesity and thyroid disorders are two common conditions, with an intriguing relationship between the two entities [19]. It remains con-

troversial whether TD led to weight change or weight change led to TD [20]. Both groups of our subjects were overweight, and there was no statistically significant difference between them. However, the median TSH values in subjects with T2DM and AITD were elevated, in hypothyroid values. Although the available data revealed a link between thyroid disorders and body weight status, these results are not consistent. Previous studies have shown that obese individuals have higher serum TSH levels [21,22] as in our study, while others have found no significant differences [23].The reasons for elevated TSH in our study can be multiple. The first, which is perhaps the most obvious, is inadequate hormonal substitution. We must consider it hypothetically because the substitution courses of hypothyroidism are not considered here. Also, one reason is related to the assumption that obesity may induce or even manifest as an autoimmune process and it is reasonable to argue that the high TSH levels found in obesity can be attributed in part to silent autoimmune thyroiditis [24]. One of the causes of high TSH in our country, and perhaps the most striking, is the coexistence of TSH of our subjects in conditions of inadequate glycemic control (PGN, PPG, HBA1c) and which are much worse in the group with AITD and hypothyroidism compared to their euthyroid control.

We found a significant association between TSH and glycemic control parameters (2h ppPG and HbA1c) and which were significantly worse in the AITD group. As with us in the study Ardekani et al. HbA1c values were significantly higher in patients with diabetes who have thyroid disorder [25]. Such TSH values may be due to the detrimental effects of chronic hyperglycemia on the hypothalamic-pituitary axis where the nocturnal peak of TSH is blunted or simply abolished [26]. Hyperglycemia also prevents deiodination of T4 to T3 in the periphery by reducing thyroxine deiodinase activity [27], which is one significant cause of thyroid dysfunction in patients with diabetes.

We noted that in all our patients in the AITD group, with poor glycemic control, thyroid dysfunction developed after the diagnosis of diabetes. The median duration of diabetes in our patients was more than 5 years, which may be an indication that longer duration of diabetes is also a risk factor for thyroid dysfunction in T2DM. This is consistent with the findings of Telwani et al. who report that the prevalence of thyroid disorders was significantly higher in diabetics with a diabetes duration of 5 years compared with a duration of less than 5 years [28]. Also, another marker of visceral obesity (abnormal waist circumference) showed that there was a statistically significant difference between subjects and controls. This is similar to the study by Udonta et al. who reported that waist circumference has a significant association with thyroid dysfunction [29]. In adult euthyroids participating in the National Health and Nutrition Survey 2007/2008, BMI and waist circumference were positively correlated with TSH levels but not FT4 [30]. In contrast, a statistically significant negative association between body mass index, FT4, was found in our study. Also, Yin et al reported a negative association between FT4 and BMI [31] as in our study, in contrast to Lundback et al. who did not find any association between adiposity and FT3 or FT4 [32].

However, these studies were on relatively small samples, such as ours, which may explain their contrasting conclusions. Therefore, more extensive studies of the relationship between TSH, FT3 and FT4 secretion with body weight in the general population are needed. Prospective longitudinal studies with the inclusion of all markers of thyroid function along with the basic components of the metabolic syndrome would be of great importance in the future.

The disadvantage of our study is the modest sample size and its inconsistency which may have affected the correlation between the components of the metabolic syndrome and the TD marker. Also, not all parameters of metabolic control were considered. Also, the study was performed as a case control study, and the cause and consequences of these relationships could not be determined. Large prospective studies are needed in the future to assess thyroid dysfunction in patients with diabetes, clarify its adverse effects, and determine their interrelationship.

CONCLUSIONS

The research has shown that thyroid function significantly correlates with certain components of the metabolic syndrome and, in line with these results, supports the existing literature reporting on metabolic control risk factors in T2DM and TD. The duration of diabetes (> 5 years) significantly precipitates in the distribution of thyroid disorders, primarily autoimmune hypothyroidism. IT has been found that female gender, central obesity, poor glycemic control are significant risk factors for thyroid dysfunction in a patient with T2DM. The study proved a significant correlation between thyroid hormones, female sex, and BMI, as well as markers of glucose dysfunction.

Dysglycemia significantly contributes to thyroid dysfunction in patients with diabetes. Although there was no evidence of an association between thyroid status and all components of MetS, TD should be considered in the assessment and treatment of patients with T2DM. Early diagnosis and treatment of even mild forms of functional thyroid disorders are important to most patients, because in this way avoided are complications and reduced morbidity and mortality especially patient who have poor glycemic control and coexisting thyreoid disease.

The given prevalence of TD in T2DM is worrying ("epidemic of thyroid dysfunction in diabetes"), especially hypothyroidism, TSH testing should be a "conditio sine qua non" and a condition by which we will actually begin monitoring and treatment of T2DM. Even routine annual testing should be considered, especially in patients with T2DM over the age of 50 with dysregulation of metabolic parameters (BMI and OS) and significant glycemic dysfunction. This is especially important in daily clinical work so as not to miss the signs and symptoms of TD.

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