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Research Article

Autoimmune Thyroid Disease in Women with Type 1 Diabetes is Associated with a Lower Incidence of Diabetic Retinopathy

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Abstract

Objectives: Our aim was to identify the correlation between autoimmune thyroid diseases (AITD) and the prevalent of diabetic retinopathy (DR) in women with diabetes mellitus type 1 (DM1).

Methods: We reviewed medical records adults women with type 1 diabetes diagnosed on the basis of WHO criteria - lasting at least a year and with AITD for at least a year. The control group consisted of women without AITD, selected according to age, BMI, DM1 duration and metabolic control. Anthropometric parameters, parameters of diabetes metabolic control, thyroid and metabolic status and presence of DR were assessed. Logistic regression analysis was used to assess the relationship between AITD and prevalent DR.

Results: We included 122 women with type 1 diabetes aged 36 ± 13 years. The average duration of DM1 was comparable between the groups, in the study group was 12 ± 10 years, and in the control group 13 ± 9 years. The parameters of metabolic control of DM as HbA1c percentage, the lipid profile and blood pressure did not differ significantly between the study groups. Patients from the study group had significantly higher concentration of TSH, fT4, anti-TPO and anti-Tg than the control group.

Conclusion: After excluding the recognized risk factors for DR in women with DM1 and concomitant AITD, showed a significantly lower chance of developing non-proliferative DR, therefore in this group of patients it is recommended to have standard assessment of TSH and thyroid antibodies levels for the early diagnosis of AITD and possible levothyroxine treatment.

Keywords: Diabetes Type 1; Women; Autoimmune Thyroid Disease; Diabetic Retinopathy; Hashimoto's Thyroiditis; Graves-Basedow' Disease

Introduction

Chronic hyperglycemia, a hallmark of diabetes mellitus (DM), resulting from disorders of insulin secretion or action, is associated with damage, dysfunction or failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels [1]. In the foreseeable future, DM is going to be one of the most important health problems, as the number of patients is expected to increase by several dozen percent. In 2017, over 424 million patients with DM were recorded worldwide. It is estimated that by 2045 the number of patients may reach 628 million [2]. Diabetic retinopathy (DR) is a microvascular complication of DM that affects a third of all DM patients worldwide. It is characterized by ischemia induced damage to the retinal microvessels and increased capillary permeability [3]. It has been shown that women with diabetes mellitus type 1 (DM1) are less likely to develop DR than men [4]. Further, sexual dimorphism is observed as younger women are more likely

to develop DR in the early stages of diabetes, and men are more at risk later in life [5,6]. Autoimmune diseases, in which the immune system produces antibodies against its own tissues, causes organ damage and the development of chronic inflammation [7]. In recent years, they have become a growing health problem in highly developed countries, especially since they are diseases that affect young, professionally and socially active people [8]. Autoimmune thyroid diseases (AITD) include Graves-Basedow' Disease (GBD) and chronic lymphocytic thyroiditis, Hashimoto's thyroiditis (HT). It is estimated that the incidence rate of HT amounts to 5% of the population, and this disease affects women 8 to 9 times more often than men [9,10]; the data suggest the role of sex hormones in the pathogenesis of the disease [8,11]. There are only a few reports in the literature on the influence of AITD on the development and progression of DR in women with DM1.

Aim of the Study

To carry out evaluation the incidence of DR in women with DM1 and AITD.

Materials and Methods

The retrospective, cross-sectional and non-interventional study was conducted in a women population with diagnosed DM 1 based on World Health Organization (WHO) criteria. The clinical research centre for this particular investigation was the Department of Endocrinology, Diabetology and Internal Diseases in Olsztyn. The medical records of hospitalized women between 2015 and 2020 were analyzed. The inclusion criteria for the study were: DM1 lasting at least a year, AITD diagnosed at least a year prior on the basis of a positive antithyroglobulin antibodies (ATA) titer and ultrasound image of the thyroid gland, age above 18 years. The study excluded patients with genetically determined diseases, refractory hypertension treated with three or more antihypertensives, systemic diseases, NYHA stage III and IV heart failure, chronic respiratory diseases, liver failure, eGFR kidney failure <30 ml/min, tumors, mental illness, alcohol abuse and/or drug addiction. The control group consisted of patients without AITD appropriately matched for age, BMI, diabetes duration and metabolic control. All procedures were performed in accordance with the ethical standards of the Bioethical Committee of School of Medicine, University of Warmia and Mazury in Olsztyn, Poland and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The research methods used in diagnosis of DM metabolic control, thyroid metabolism, AITD and DR included clinical, physical examination, blood pressure (BP), laboratory, biochemical, hormonal concentrations tests and statistical. Data on the date of birth, decade of DM1 diagnosis, and years of DM1 until the last follow-up were extracted. Other data extracted for analysis included history of hypertension and dyslipidemia. The diagnosis of hypertension was considered based on medical records if any the following criteria were met: (1) the patient was taking anti-hypertensive medications; (2) the patient had been diagnosed with hypertension regardless of treatment status. The diagnosis of dyslipidemia was considered the diagnosis was considered based on medical records if any of the following criteria were met: (1) the patient was taking lipid-lowering medications; (2) the patient had been diagnosed with dyslipidemia regardless of treatment status. We also extracted information regarding the available body mass index estimates (kg/m^2), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) evaluations for each individual and averaged. The Laboratory of the Provincial Hospital in Olsztyn was an experimental research centre, where biochemical and hormonal concentrations tests were evaluated in serum by enzymatic-calorimetric and electrochemiluminescence methods. Data regarding laboratory parameters were also collected. For the following variables, the measurements at the follow-up for each patient were averaged and inputted for analysis: glycated hemoglobin (HbA1c), total cholesterol (TC) high-density lipoprotein, (HDL - cholesterol), low-density lipoprotein, (LDL - cholesterol), triglyceride (TG), and creatinine with evaluation of estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula, free thyroxine (fT4), free triiodothyronine (fT3) and pituitary hormone - thyroid-stimulating hormone (TSH), ATA titers: antithyroid peroxidase antibodies (aTPO), antithyroglobulin antibodies (aTG) and TSH receptor autoantibodies, (anti-TSHR, TRAb). Women also done thyroid gland ultrasounds. DR status was diagnosed and classified on the basis of fundoscopy performed by an ophthalmologist. DR stadiums were assessed on the basis of the criteria of International Clinical Classification for Diabetes Retinopathy, as no DR, Non-proliferative Diabetes Retinopathy (NPDR) or Proliferative Diabetes Retinopathy (PDR) [12,13]. People with panretinal photocoagulation were also included in the PDR group. If there was asymmetric retinopathy, the eye with the worst condition was used for classification. Statistical analysis.

Continuous variables were expressed as mean and standard deviation (mean ± SD). Qualitative data are presented as structure indicators (%). The assessment of the normality of the distribution of obtained results was based on the Shapiro-Wilk test. Student's t-test was used to assess the statistical significance of differences

between the examined groups. If the variables did not meet the normality criteria, the Mann-Whitney U test was performed. Logistic regression analysis was used to analyze the association between AITD and DR. The odds ratio (OR) and 95% Confidence Interval (CI) were calculated utilizing logistic regression analysis. The level of significance was set at $\alpha = 0.05$. The data were analyzed using the statistics software Statistica 13.3 PL program for Windows.

Results

In the study, hospital records of 122 women aged 36 ± 13 were analyzed. The mean duration of DM1 in the whole group was 14 ± 10 years, and the HbA1c rate was 8.4 ± 2%. The study group consisted of 79 women diagnosed with DM1 and AITD, aged 36 ± 13. The control group consisted of 43 women with DM1 without AITD, matched according to age, BMI, diabetes duration and metabolic control, aged 36 ± 13. The average duration of DM1 in the study group was 12 ± 10 years, and in the control group 13 ± 9 years. The parameters of metabolic control of DM as HbA1c percentage, the lipid profile and blood pressure did not differ significantly between the study groups. The concentration of TSH, fT4, anti-TPO and anti-Tg was significantly higher in the study group than in the control group. The obtained data are presented in table 1-3.

The frequencies of NPDR were different among the groups when TSH level was 0.4 - 2.5 mU/l. Despite the same thyroid status, NPDR was significantly more common in the group without AITD ($p < 0.01$). NPDR was the most common when TSH level was 0.4 - 2.5 mU/l and were not higher in those with higher TSH levels. PDR was the most common when TSH level was more than 2.5 mU /l (Table 4).

Parameters	Study group	Control group	p
Number of patients (n)	79	43	
Age (years)	36 ± 13	36 ± 13	0.94
Duration of DM1 (years)	13 ± 11	15 ± 8	0.12
BMI (kg/m^2)	24.31 ± 4	23.13 ± 3	0.07
Creatinine (mg/dl)	0.72 ± 0.2	0.71 ± 0.2	0.76
eGFR (ml/min/1.73 m^2)	98.79 ± 28.4	101.19 ± 26.8	0.68

Table 1: Characteristics of both groups. Study group: DM 1 + AITD. Control group: DM 1 without AITD. P < 0.05 study group vs control group.

Parameters	Study group	Control group	p
SBP (mmHg)	115 ± 12	113 ± 9	0.06
DBP (mmHg)	75 ± 9	77 ± 7	0.08*
HbA1c (%)	8.2 ± 2	8.8 ± 2	0.10
TC (mg/dl)	188 ± 45	183 ± 39	0.31
LDL-c (mg/dl)	110 ± 40	103 ± 30	0.05
HDL-c (mg/dl)	73 ± 18	73 ± 25	0.83*
TG (mg/dl)	95 ± 49	110 ± 54	0.50

Table 2: Parameters of DM metabolic control: Study group: DM 1 + AITD. Control group: DM 1 without AITD. P < 0.05 study group vs control group. *: Mann-Whitney U test.

Parameters	Study group	Control group	p
TSH (mU/l)	2.61 ± 5.39	2.02 ± 0.77	<0.01
fT3 (pmol/l)	4.39 ± 1	4.36 ± 0.83	0.18
fT4 (pmol/l)	16.99 ± 3.91	15.35 ± 2.24	<0.01
aTPO (IU/ml)	199 ± 177	16 ± 8	<0.01
aTg (IU/ml)	192 ± 257	19 ± 18	<0.01

Table 3: Thyroid function assessment. Study group: DM 1 + AITD. Control group: DM 1 without AITD. P < 0.05 study group vs control group.

In the study group, 12 (15.19%) women had NPDR and 3 (3.8%) PDR (Figure 1).

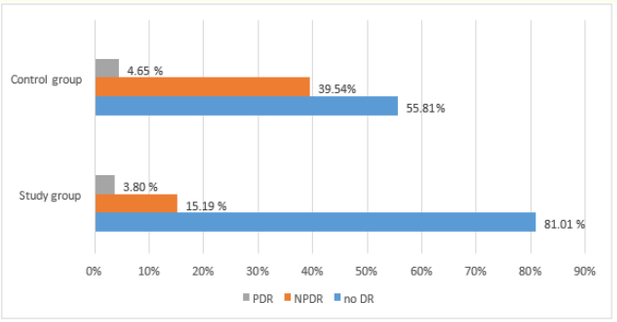

Figure 1: Occurrence of DR. p <0.01 *. Study group: DM 1 + AITD. Control group: DM 1 without AITD. Study group vs control group. * chi-square test.

TSH (mU /l)		Study group				Control group			p*
	n (%)	No DR n (%)	NPDR n (%)	PDR n (%)	n (%)	No DR n (%)	NPDR n (%)	PDR n (%)	
<0.4	5 (6.33)	5 (100)	0 (0)	0 (0)	1 (2.33)	0 (0)	0 (0)	1 (100)	0.619
0.4-2.5	44 (55.7)	37 (84.09)	6 (13.64)	1 (2.27)	31 (72.09)	15 (48.39)	15 (48.39)	1 (3.22)	<0.01
> 2.5	30 (37.97)	22 (73.33)	6 (20)	2 (6.67)	11 (25.58)	9 (81.82)	2 (18.18)	0 (0)	0.211

Table 4: Frequency of DR according to TSH levels. Study group: DM 1 + AITD. Control group: DM 1 without AITD. Study group vs control group. *: Chi-square test.

Logistic regression analysis was used to determine the relationship between the effect of AITD in women with DM1 and the presence of DR. Women with DM1 with AITD showed a significantly lower chance of NPDR than in the control group. The relationships are presented in table 5 and 6.

	Odds ratio (95% CI)
Study group	1.778 (0.2728 - 11.5873)
Control group	1
p	0.55

Table 5: OR of PDR in women in the study group (DM 1 + AITD) and in the control group with DM 1 without AITD.

	Odds ratio (95% CI)
Study group	0.265 (0.1093 - 0.6412)
Control group	1
p	< 0.01

Table 6: OR occurrence of NPDR in women in the study group (DM 1 + AITD) and in the control group with DM 1 without AITD.

Discussion

DM has nowadays become a major cause of adult blindness, renal failure and limb amputation, as well as a major risk factor for coronary heart disease and heart attack, stroke, and birth defects in newborns. It shortens the average life expectancy by an average of 10 - 15 years [14]. Complications that are a consequence of chronic DM are the main and still growing problem in patients suffering from this disease. Probability of occurrence of DR among patients diagnosed with DM before 30 years of age is estimated at 50% after 10 years of suffering from the disease, and at as much as 90% after 30 years [15]. The most obvious and most important predictor of the development and progression of DR is chronic hyperglycemia. The Diabetes Control and Complications Trial clearly showed that high-intensity glycemic control can reduce DR incidence by 76% and DR progression by 54%. Other major risk factors for DR include diagnosed hypertension, dyslipidemia, and high BMI. Moreover, the risk of development and progression of DR is influenced by a number of non-modifiable risk factors, such as the duration of diabetes, pregnancy, puberty and population diversity [16]. It has been shown that thyroid disease occurs in 13.4% of patients with DM, with women with DM1 (31.4%) noted most often [17]. Though, the effect of thyroid diseases, including AITD on DR occurrence is still unknown. In our previous retrospective cross-sectional study, we showed that the coexistence of AITD in patients with DM1 is associated with a lower risk of NPDR dissemination. However, the study group was not matched for gender and metabolic control of DM, which could have influenced the test results [18]. This prompted us to analyze the prevalence of DR in the solely female population, as they are at greater risk of coexisting AITDs. These differences were established primarily based on the results of our current research and the review of related literature. Diabetes duration, systolic and diastolic blood pressure, and HbA1c levels in the study with only female participants did not differ significantly between the groups (cf. table 1 and 2). In the analyzed group of 122 women with DM1, the average duration of DM1 was 14 ± 10 years. The longest duration of the disease was 42 years. The interview data show that all patients were diagnosed with DM1 and were treated with insulin from the beginning. The HbA1c percentage in the study group was 8.2 ± 2%, and in the control group 8.8 ± 2%. The influence of the menstrual cycle on glycemia is difficult to characterize, but most studies of women with DM1 monitored with CGMs have shown an increased incidence of hyperglycemia in the luteal phase [19]. However, in women with DM, the female gender ceases to be a protective factor which causes an even greater frequency of complications of DM when compared to men. This phenomenon is not fully understood, however the differences are probably fostered by the imbalance of sex hormones [20,21]. Women with DM1 have delayed menarche, suffer from sexual dysfunctions and menstrual irregularities, are at high risk of complicated pregnancies, and go through menopause at an earlier age compared with women without DM [22,23]. Few studies have determined the level of sex hormones in women with DM1 and no attempt has been made to investigate the direct influence of sex hormones on the development of vascular complications, including DR [24,25]. It should be emphasized that pregnancy is an independent risk factor for DR which suggests the role of sex hormones in its development [26]. Pregnancy is a condition in which the function of the woman's immune system is also modified. It is widely believed that female immune system is immunosuppressed during pregnancy. However, a phenomenon that becomes more often discussed nowadays is immunomodulation and changes in the immune response in pregnancy [27,28]. The causes of this phenomenon have not been identified so far. DM1 and DM2 both affect the vessels and the nervous system. DR is mainly assessed on the basis of vascular changes observed via fundus ophthalmoscopy, however, it is preceded by neuropathy [29]. Our study found that in 81.01% of patients in the study group and 55.81% in the control

group no changes at the fundus. 18.99% of patients in the study group and 44.19% from the control group were diagnosed with DR with varying degrees of severity. NPDR exponents were found in 15.19% of patients with DM1 and AITD and 39.54% of patients without AITD. PDR was diagnosed in 3.8% of patients. Autoimmune diseases are multifactorial disorders characterized by endothelial dysfunction of the blood vessels. Inflammation within the blood vessels causes a reduction in the elasticity of their walls, narrowing of the lumen of the arteries, reduced blood flow and, consequently, the development of atherosclerosis [30]. Examining euthyroid patients with AITD, Zhang., *et al*. noted that damage to the arterial endothelium is correlated with the concentration of aTPO which indicates the participation of the immunization process in the generation of atherosclerotic lesions [19]. Moreover, it was observed that patients with normal thyroid function after a stroke with intracranial vasoconstriction showed an elevated titer of aTPO antibodies, while the majority of patients without pathological changes in intracranial vessels had normal thyroid autoantibody titer [31]. Treatment of thyroid dysfunction is very important in DM patients. It was shown that has a beneficial effect on glycemic control, reduces cardiovascular risk, and improves patients' overall well-being [32]. Literature analysis of the occurrence of DR in patients with DM1 shows a significant impact of thyroid disease on the development of DR. By examining the DM1 patient population, including 477 men and 721 women in Brazil, Rodacki M., *et al*. have proved that TSH levels at 0.4-2.5 mU/L are associated with a lower risk of DR and renal failure in people with DM1, regardless of glycemic control and duration diseases [33]. In our study TSH levels in the study group was 2.61 ± 5.39 mU/L and in the control group 2.02 ± 0.77 mU/L. In the study group the levels of TSH was higher than in the control group, so it was not a protective factor in this group. However, Rogowicz-Frontczak A., *et al*. showed interesting conclusions, that patients with type 1 DM and positive aTPO, aTg or TRAb antibodies (women/men accordingly 19/12) develop microangiopathy to a lesser extent when compared to a group without AITD [34]. In the study group, all patients were treated with levothyroxine. It would be interesting to analyze whether AITD and levothyroxine preparations have a positive effect on reduce the risk of developing DR. In the case of endothelial dysfunction in women, the role of estrogens in modulating vascular function is emphasised. Estrogen receptors are distributed throughout the body, including the vascular endothelium and the vessel wall [35]. Hyperglycemia adversely alters the expression balance and activity of estrogen receptors, and this diverse expression can be gender specific. Experimental studies in rats induced by streptozotocin have shown that DM is associated with an increase in ERα in the kidneys (but not Erβ and only in females) [36]. However, whether similar sexspecific regulation of estrogen receptors occurs in DM in other organs, including the vascular system, remains unexplored. The differential expression of estrogen receptors may lead to impaired estrogen function in hyperglycemic conditions and may be one of the reasons for the inability to state that female sex is a predictor of DM complications. According to the literature, the prevalence of ATA in children with DM1 is 3-50%. The incidence of ATA in patients with DM1 ranges from 15-30%. They are more common in women and their presence is associated with a longer duration of DM [37]. Based on our recent study, a question has been asked whether the above-mentioned phenomenon also occurs in the population of women who are more likely to develop AITD. To the best of our knowledge, the available literature currently does not include studies on the development and progression of DR and the prevalence of AITD in women with type 1 DM. Analyzing the limitations of the last study, female patient population was selected taking into account already recognized risk factors for DR. The study demonstrated a higher prevalence of NPDR in the group of women without AITD. This amazing discovery has been confirmed in the female population alone so far. Naturally, it requires further research on a larger group of patients in order to fully analyze the exact mechanisms of correlations and relationships. That would improve the diagnosis of treatment and prevention of vascular DM complications, including DR.

Conclusion

Based on the research results obtained, after excluding the recognized risk factors for DR in women with DM1 and concomitant AITD, a significantly lower chance of developing non-proliferative DR was demonstrated, therefore in this group of patients it is recommended to have standard assessment of TSH and ATA levels for the early diagnosis of AITD and initiation of levothyroxine preparations treatment.

Conflict of Interest

The authors declare that there is no conflict of interest associated with this manuscript.

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