EPIDEMIOLOGICAL ASPECTS OF AUTOIMMUNE CHRONIC THYROIDITIS IN A GROUP OF ADULTS WITH THYROID DISEASES AND DIABETES MELLITUS AND OTHER CHANGES IN GLYCEMIC BALANCE

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Abstract

Background&Aims: Autoimmune chronic thyroiditis (ACT) is frequently associated with diabetes mellitus (DM) in clinical practice. The purpose of this study is to assess the prevalence of ACT in a group of adults with DM and other changes in glycemic balance.

Methods: The studied group was of 650 people with DM and other changes in glycemic balance, aged between 18 - 79 years. The methods of investigation were represented by clinical, imaging, biochemical, hormonal and immunological parameters.

Results: The prevalence of ACT in the study group was 32% (33.33% F and 19.35% M, $p = 0.024$, $X^2 = 5.04$). ACT prevalence was 83.33% for DM type 1 (85.45% F and 60% M, $p = 0.143$, $X^2 = 2.14$), 26.55% for DM type 2 (27.38% F and 21.05% M, $p = 0.41$, $X^2 = 0.68$), 28.41% for impaired glucose tolerance (IGT) (29.47% F and 10% M, $p = 0.184$, $X^2 = 1.76$), and 24.78% for impaired fasting glucose tolerance (IFG) (26.85% F and 0% M, $p = 0.07$, $X^2 = 3.21$). Significant differences regarding ACT prevalence were found between the group with DM type 1 and type 2 and other changes in glycemic balance (83.33% vs. 26.55%, $p < 0.001$, $X^2 = 69.33$ for type 2 diabetes, 83.33% vs. 28.41%, $p < 0.001$, $X^2 = 55.95$ for IGT, 83.33% vs. 24.78%, $p < 0.001$, $X^2 = 55.01$ for IFG).

Conclusion: ACT has prevailed in females and in the group with type 1 diabetes due to autoimmune origin, part of the polygalndular autoimmune syndrome type III.

Keywords: Autoimmune chronic thyroiditis, diabetes mellitus, other changes in glycemic balance, prevalence, adults

Introduction

Thyroid disorders are frequently associated with diabetes in clinical practice. In type 1 diabetes, because autoimmune etiology it is often associated with autoimmune thyroid disease (chronic autoimmune thyroiditis, Basedow-Graves disease).

Hashimoto's thyroiditis is a condition caused by inflammation of the thyroid gland. It is an autoimmune disease, which means that the body inappropriately attacks the thyroid gland--as if it was foreign tissue. The underlying cause of the autoimmune process still is unknown. Hashimoto's thyroiditis tends to occur in families, and is associated with a clustering of other autoimmune conditions such as type 1 diabetes, and celiac disease. Hashimoto's thyroiditis is 5-10 times more common in women than in men and most often starts in adulthood. Blood drawn from patients with Hashimoto's throiditis reveals an increased number of antibodies to the enzyme, thyroid peroxidase an enzyme (protein) found within the thyroid gland. As result of the antibodies' interaction with the enzyme, inflammation develops in the thyroid gland, the thyroid gland is destroyed, and the patient ultimately is rendered hypothyroid (too little thyroid hormone).

The disease begins slowly. It may take months or even years for the condition to be detected. Chronic thyroiditis is most common in women and people with a family history of thyroid disease. It affects between 0.1% and 5% of all adults in Western countries.

Hashimoto's disease may, in rare cases, be associated with other endocrine disorders caused by the immune system.

Hashimoto's thyroiditis is the most common cause of hypothyroidism in the United States.

Hypothyroidism is very common and is estimated to affect 3%-5% of the adult population. It is more common in women than in men, and the risk of developing hypothyroidism increases with advancing age (Hypponen et al, 2000).

Because patients with organ-specific autoimmune disease are at risk of developing other autoimmune diseases, and thyroid disorders are more common in women, it is not surprising that 30% of women with type 1 diabetes presents thyroid damage. Postpartum thyroiditis rate in diabetic patients is three times higher than in healthy women (Hypponen et al, 2000).

Type 1 diabetes is commonly associated with endocrine and systemic disease with autoimmune etiology as Graves-Basedow disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, pernicious anemia, myasthenia gravis, vitiligo, etc. (Armengol et al, 2003).

From people with type 1 diabetes, ≈ 1-20 patients are generally affected by hypothyroidism (Diabetes Prevention Program Research Group,

2002). The frequency of DM type 1 association with hypothyroidism varies from 0.7% to 4% (American Diabetes Association, 2001).

A particular association of DM type 1 with hypo-or hyperthyroidism, is characteristic to polyglandular autoimmune syndrome (PAS). There are 3 polyglandular autoimmune syndromes.

Polyglandular autoimmune syndrome type I (PAS I) is a recessive autosomal disorder caused by a mutation on the short arm of chromosome 21, characterized by the triad of mucocutaneous candidiasis, hypoparathyroidism and Addison's disease (Aldasouqi et al, 2006, Myhre et al, 2001).

Polyglandular autoimmune syndrome type II (PAS II) (Sivarajah et al, 2006, Betterle et al, 2004) is the most common immunoendocrinophathy. It occurs in adulthood, affecting mostly women. It is characterized by the appearance in the same person of two or more of the following diseases: Addison's disease, Graves-Basedow's disease, thyroiditis with autoimmune etiology, type I diabetes mellitus, primary hypogonadism, myasthenia gravis, celiac disease.

Polyglandular autoimmune syndrome type III (PAS III) (Aung et al, 2006) is a PAS II syndrome without adrenocortical involvement. It comprises a group of autoimmune disorders generally characterized by glandular insufficiency. One fourth of the patients with the hypofunction of one gland present other endocrine glands hypofunction, too. This syndrome is associated with the following diseases: celiac disease, hypogonadism, myasthenia gravis, sarcoidosis, Sjogren's syndrome, rheumatoid arthritis, gastric cancer, malabsorption due by pancreatic exocrine deficiency time, and can be classified into 3 categories:

- PAS type III a - autoimmune thyroiditis with DM type 1
- PAS type III b - autoimmune thyroiditis with pernicious anemia
- PAS type III c - autoimmune thyroiditis with vitiligo and/or alopecia and/or other autoimmune diseases

In the case of associations between IGT and IFG with thyroid diseases, these usually appear as thyroid hormones excess. These associations are more frequently at women.

In a US study it is show that in the patients with thyroid diseaseses, glucose intolerance was present in 38% cases, and incidence of clinical diabetes was ≈ 2-3 % (Wartofsky, 2000, Werner et al, 2000).

Another authors show a prevalence of thyroid diseases at patients with DM type 2 at 2.5%, the most freuently thyroid disease being subclinical hypothyroidism (4,1%) (Radaideh et al, 2004).

Material And Methods

Investigated population

650 people with diabetes and other changes in glycemic balance (588 F and 62 M) aged between 18 and 79 years represented the study group.

Depending on glycemic balance the group was divided into:
- The group with DM type 1 - 60
- The group with DM type 2 - 290
- The group with IGT - 183
- The group with IFG – 117

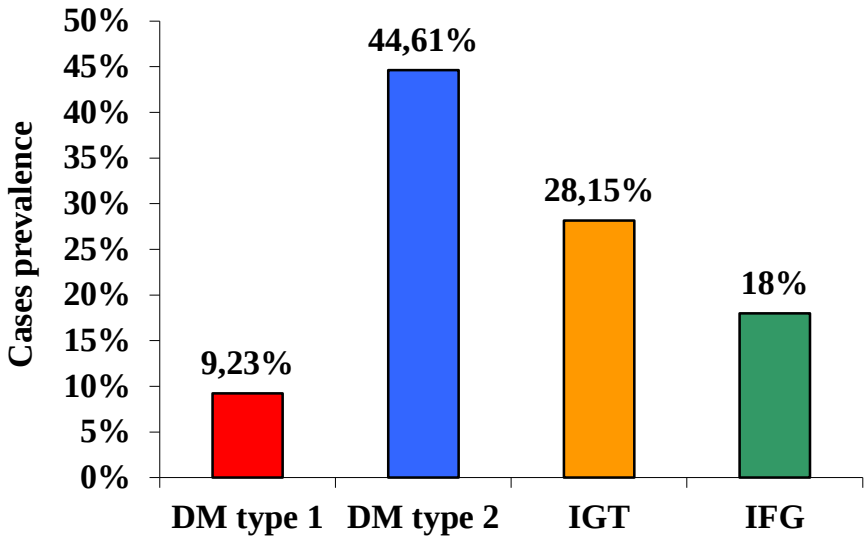

Figure 1. Cases distribution according to the type of changes in glycemic balance

Methods of investigation

The methods of investigation were represented by **clinical data** - case history, current status, **imagistic**- thyroid ultrasound, **biochemical** - ***for glycemic balance***: fasting blood glucose, glycosylated hemoglobin, ***investigation of the thyroid gland***: TSH, FT_4, FT_3, thyroid antibodies.

Determination of plasma glucose was performed by enzyme technique with glucosooxidasis. Normal values were taken between 70 - 110 mg%; diabetes mellitus - values equal or over 126 mg%, impaired glucose tolerance - values between 110 - 125 mg% and the OGTT at 2 h between 140 - 200 mg% and impaired fasting glucose - values between 110 - 125 mg% and OGTT at 2 h under 140 mg%.

Determination of HbA1c was achieved through the DiaStat for measuring HbA1c reported to the total HbA.

To determine ***the TSH level in plasma, the free fraction of triiodotironin (FT_3), and the plasma free fraction of thyroxin (FT_4)*** were performed a quantitative method ARCHITECT; witch is an immunological method, Chemilumnescent Micro particle Immunoassay (CMIA). Normal values were following: TSH = 0.465-4.68 Miu/ml, FT_3 = 3.69 -10.4 pmol/l, FT_4 = 10-28.2 pmol/l.

The immunological parameters were represented by autoimmune thyroid markers - antibodies (antiTPO and antiTg antibodies).

To determine ***serum levels of antiTPO antibodies*** it was used the kit AxSYM antiTPO, an immunological method (Micro particle Enzyme Immunoassay) (MEIA). Normal values: antiTPO antibodies <35 IU/ml.

To determine ***serum levels of antiTg antibodies*** it was used the kit AxSYM antiTg, a MEIA method as well (Micro particle Enzyme Immunoassay). Normal values: antiTg antibodies <55 IU/ml.

Thyroid ultrasound was performed in all cases and allowed us to measure thyroid volume, thyroid study and the changes in parenchyma's density.

An increased density, uniform, characterizes normal thyroid parenchyma easily distinguished from the neck muscles that are hypo dens.

Inflammatory processes and autoimmune pathology appears hypo dens**.** The scale was assessed as being discreet +, moderate ++ and marked +++.

In the autoimmune thyroid disease the parenchyma of the gland appears hypo dens.

Chronic autoimmune thyroid disorder appears with a hypoecogenity of the parenchyma and normal or increased thyroid volume.

Statistical analysis

For statistical analysis we used Microsoft Excel and POP Tools from Microsoft Office 2003 and EPI 2000 program. To measure the quantitative variables were determined average and standard deviation, and to assess the gender differences and other differences we used the unpaired t test and ANOVA test, considering statistically significant a $p < 0.05$.

Results and discussion

Adults group included 650 people, young adults, adults and the elderly, aged between 17 and 79 years (Table I). It consisted of subjects with diabetes which in time present thyroid diseases and subjects with thyroid disease who have developed glucose metabolism disorders or diabetes.

Table I. Distribution according to age and gender of adults group

Age	Cases number		Female		Male	
	n	%	n	%	n	%
18 – 19 years	11	1.7	10	90.9	1	9.1
20 – 29 years	29	4.46	27	93.1	2	6.9
30 – 39 years	48	7.38	43	89.58	5	10.42
40 – 49 years	168	25.84	141	83.93	27	16.07
50 – 59 years	219	33.7	209	95.43	10	4.57
60 – 69 years	118	18.15	112	94.91	6	5.09
70 – 79 years	57	8.77	46	80.7	11	19.3

Adults group was subdivided according to the type of change in glycemic balance in four subgroups (Fig. 1):

- group with DM type 1 with 60 cases (9.23%)
- group with DM type 2 with 290 cases (44.61%)
- IGT group with 183 cases (28.15%)
- IFG group with 117 cases (18%)

DM type 1 represent 5 – 10 % from all cases with DM (1.4 million persons in US and 10 – 20 millions persons in all the world). (Şerban V, 2010)

More than half DM type 1 cases are diagnosed after 15 years. In adult, most DM type 1 cases are mask by a false diagnostic of DM type 2, for a long or a short period of time. (Şerban V, 2010)

Information about DM type 1 incidence are little, but its incidence decrease in the 3rd decade of life and increase between 5 and 7 decade of life. (Şerban V, 2010)

About the gender, in areas with DM type 1 higher incidence, in adult, men have a higher risk, compare with women. (Şerban V, 2010)

DM type 2 represent 90 – 95% from all cases with DM.

In the country in course of development, prevalence peak is at 40 – 45 age, while in develop country, this is above 60 years. (Şerban V, 2010)

In a study perform in Germay, in 2000, DM type 2 prevalence was 16.7% at men and 8.6% in women, between 50 -59 years, and 23.2% at men and 17% at women between 70 and 74 years. (Rathmann et al, 2003)

AusDiab study show that DM type 2 affect 2.7% of men and 2.2% of women with age between 35 and 44 years, and 23.1% from men and 22.7% from women with age above 75 years. (Şerban V, 2010)

NHANES III study reveal the same prevalence increase tendency with age: 5.9 % at men and 4.8% at women between 40 – 49 years and 19.2 % at men and 16.6% at women after 75 years. (Şerban V, 2010)

Regarding the gender, the prevalence is higher in male, in the case of population with better economic situation, from Europe and US, and a preponderence of female in the rural areas. (Şerban V, 2010)

In the study group, we had a predominance of females, because of the association of DM with thyroid disorder, diseases that prevail in women.

The current average age and the onset average age of DM in the adult's subgroups with different changes in glucose metabolism is shown in Table II.

Table II. Distribution of adult's subgroups with different changes in glucose metabolism by current age and by onset age

Para meters	Cases number	Average	Standard deviation	Median	Minimum	Maximum
DM type 1						
Onset age (years)	60	30.46	22.94	24.5	0	63
Current age (years)	60	46.08	18.95	43	18	72
DM type 2						
Onset age (years)	290	51.86	10.3	51	20	79
Current age (years)	290	55.43	10.73	54	20	79
IGT						
Onset age (years)	183	48.84	10.61	50	17	76
Current age (years)	183	49.32	10.64	51	17	76
IFG						
Onset age (years)	117	50.7	12.76	52	20	73
Current age (years)	117	50.88	12.69	52	20	73

The onset average age of type 1 diabetes corresponds with the literature, because it is known that type 1 diabetes usually occurs before 30 years. Sometimes it may appear after 30 years, being labeled initially as type 2 diabetes later prove to be a LADA type.

NHANES study estimated that the prevalence of type 1 diabetes diagnosed between 30-74 years in the U.S. population is about 0.3% (0.1% from 0.6% between 30-49 years and 65-74 years) (Karvonen et al, 2003).

The group of adults with type 2 diabetes included 290 people, young adults, adults and the elderly, ages 20 -79 years.

The onset age of type 2 diabetes corresponds with the literature, because it is known that type 2 diabetes usually occurs after 40 years. DECODE study showed that in Europe type 2 diabetes met frequently

between 40-59 years, incidence was higher in women and in the white population (The DECODE Study Group, 2003). AusDiab study showed that the prevalence of type 2 diabetes increases with age, from 2.7% in men and 2.2% in women between 35-44 years to 23.5% and 22.7% at 75 years and over (Dunstan et al, 2002). Also, in the Mexican population, the prevalence of type 2 diabetes increases from 4.2% and 3.2% for men and for women between 35-39 years at 23.1% for men and at 41.7% for women between 60-64 years (Qiao et al, 2004).

Adults group with IGT involving 183 people, young adults, adults and elderly, aged 17-76 years.

Adults group with IFG included 117 people, young adults, adults and the elderly, ages 20 -73 years.

The prevalence of IGT and IFG in Europe and Asia was assessed by 2 studies: DECODE and DECODA. In Europe, the prevalence of IGT was less than 15% between 30-59 years and 30% over 60 years. IGT incidence increases linearly with age, while IFG not (Qiao et al, 2004).

The prevalence of ACT in the study group was 32% (33.33% F and 19.35% M, $p = 0.024$, $X^2 = 5.04$).

ACT prevalence in type 1 diabetic group was 83.33% (85.45% F and 60% M, $p = 0.143$, $X^2 = 2.14$), 26.55% in type 2 diabetic group (27.38% F and 21.05% M, $p = 0.41$, $X^2 = 0.68$), 28.41% in IGT group (29.47% F and 10% M, $p = 0.184$, $X^2 = 1.76$), and 24.78% in IFG group (26.85% F and 0% M, $p = 0.07$, $X^2 = 3.21$).

In the case of Hashimoto's thyroiditis, at adult, the incidence is estimated at 3.5 for women and 0.8 /1.000/year at men. The incidence is higher in geographic areas with adequate or increased intake of iodine and limited in ones with iodine deficiency.

A number of studies show the association between thyroid disease with diabetes and other changes in glycemic balance. The most common thyroid disorders are autoimmune ones in type 1 diabetes and these accompanied by thyrotoxicosis for type 2 diabetes and other changes in glycemic balance.

A study in the Czech Republic shows that the prevalence of thyroid disease in patients with diabetes is 2-3 times higher than in non-diabetic patients (Sivarajah et al, 2006). It increases with age and is strongly influenced by female gender and autoimmune diabetes (Sivarajah et al, 2006(.

Perros et al. (1995) showed in a study on 1310 adult patients with DM that the prevalence of thyroid disease was 13.4%, higher in women with type 1 diabetes (31.4%) and lower in men with type 2 diabetes (6.9%). Newly diagnosed thyroid disease was present in 6.8% of cases, on the first place being subclinical hypothyroidism (4.8%), followed by manifest

hypothyroidism (0.9%), subclinical hyperthyroidism (0.5%) and clinically hyperthyroidism (0.5%). Female patients with type 1 diabetes had the highest risk of developing thyroid disease (12.3%), but all the patients from the study group had a higher incidence of thyroid disease compared to the general population. This study suggests that thyroid function should be investigated in diabetic patients annually to detect asymptomatic thyroid damage with increased frequency in the diabetic population (Radaideh et al, 2006)

Regarding gender distribution, we found a predominance of females in the study group, aspect consistent with the literature as thyroid disorders are more common in women.

In the case of Hashimoto's thyroiditis, the ratio F/M was 15.6/1 in the case of the group with type 1 diabetes, 8.6/1 for DM type 2, 51/1 for IGT and 29/0 for IFG. In literature it was found that the incidence is 10 to 15 times more common in women (Orlander et al, 2005).

The distribution by onset age of thyroid disease is shown in Tab. III.

Table III. The onset average age of ACT disease in the studied group

Parameters	Cases number	Average	Standard deviation	Median
DM type 1	50	42.78	18.17	42
DM type 2	77	48.7	10.31	49
IGT	52	41.48	8.64	42.5
IFG	29	51.2	15.14	56

Thus, in the case of Hashimoto's thyroiditis, onset age is between 30-50 years in females and between 40-65 years in males [18].

Table IV. ACT duration at adult studied group

Parameters	Cases number	Average	Standard deviation	Median	Minimum	Maximum
DM type 1	50	4.3	3.98	2.5	0	12
DM type 2	77	5.57	7.49	3	0	36
IGT	52	5.07	8.11	1	0	38
IFG	29	3.51	5.69	1	0	23

Table V. The interval of appearence between ACT disease and differents changes in glycemic balance

Time interval	DM type 1	DM type 2	IGT	IFG
DM after ACT				
< 5 years	36%	63.63%	71.5%	75.6%
5 – 10 years	2%	10.33%	9.6%	1.03%
10 – 15 years	-	7.73%	7.6%	6.85%
15 – 20 years	-	2.53%	5.7%	3.44%
20 – 25 years	-	1.23%	1.92%	3.44%
25 – 30 years	-	-	1.92%	-
> 30 years	-	2.53%	1.92%	-
ACT after DM				
< 5 years	-	10.33%	-	-
5 – 10 years	14%	-	-	-

10 – 15 years	6%	-	-	-
15 – 20 years	8%	-	-	-
20 – 25 years	2%	-	-	-
25 – 30 years	24%	1.23%	-	-
> 30 years	8%	-	-	-

Regarding the interval of appearence between ACT disease and differents changes in glycemic balance, in the case of DM type 1 we found 2 situations: appearence of DM type 1 after ACT, mostly in the first 5 years and ACT after DM type at a variable period of time, due to the autoimmune origin of this 2 diaeases. In the case of DM type 2, IGT and IFG, there appear after ACT at a variable peroid of time, mostly in the first 5 years, probably because of treatment of ACT with thyroid hormones. Also, in the caee of DM type 2 we have appearence of ACT after DM type 2, but this association was random.

Significant differences regarding ACT prevalence were found between the group with diabetes type 1 and type 2 diabetes and other changes in glycemic balance (83.33% vs. 26.55%, $p < 0.001$, $X^2 = 69.33$ for type 1 diabetes and type 2 diabetes, 83.33% vs. 28.41%, $p < 0.001$, $X^2 = 55.95$ for type 1 diabetes and IGT, 83.33% vs. 24.78%, $p < 0.001$, $X^2 = 55.01$ for type 1 diabetes and IFG), but not between type 2 diabetes and other changes in glycemic balance (26.55% vs. 28.41%, $p = 0.65$, $X^2 = 0.2$ for type 2 diabetes and IGT, 26.55% vs. 24.78%, $p = 0.71$, $X^2 = 0.13$ for type 2 diabetes and IFG, 28.41% vs. 24.78%, $p = 0.48$, $X^2 = 0.48$ for IGT and IFG.

Conclusion

ACT has prevailed in females and in the group with type 1 diabetes due to autoimmune origin, part of the polyglandular autoimmune syndrome (PAS) type III A.

In the case of DM type 2, IGT and IFG, these appear after ACT, at a variable peroid of time, mostly in the first 5 years, probably because of treatment of ACT with thyroid hormones.

It is useful to determine antithyroid antibodies in patients with type 1 diabetes to detect early ACT because it may progress with hypothyroidism (risk of atherosclerosis and associated cardiovascular diseases).

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