PREVALENCE OF ASSOCIATIONS BETWEEN GRAVES - BASEDOW DISEASE AND DIABETES OR OTHER GLYCEMIC CHANGES IN AN ADULTS GROUP

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Abstract

Background&Aims: Thyroid disorders are frequently associated with diabetes in clinical practice. The purpose of this study is to assess prevalence of associations between Graves - Basedow disease and diabetes or other changes in glycemic balance in an adults group. **Methods:** The studied group was of 650 people with diabetes and other changes in glycemic balance aged between 18 and 79 years. The methods of investigation were represented by clinical, imaging, biochemical, hormonal and immunological parameters. **Results:** The prevalence of Graves – Basedow disease in the study group was 22.61% (21.76% F vs. 30.64% M, p = 0.11, X^2 = 2.53). Graves – Basedow disease prevalence for type 1diabetes was 10% (9.09% F and 20% M, p = 0.38, X^2 = 0.75), 20.68% for type 2 diabetes (21.03% F and 18.42% M, p = 0.71, X^2 = 0.14), 23.49% for impaired glucose tolerance (IGT) (23.12% F and 30% M, p = 0.61, X^2 = 0.25), and 32.47% for impaired fasting glucose tolerance (IFG) (27.77% F and 88.88% M p = 0.00016, X^2 = 14.15). Significant differences in this prevalence were found only between type 1 diabetes and other changes in glycemic balance (10% vs. 23.49%, p = 0.023, X^2 = 5.11 for IGT, 10% vs. 32.47%, p = 0.001, X^2 = 10.73 for IFG). **Conclusions:** Graves – Basedow disease was mainly associated with IGT and IFG that occurred due to the presence of excess thyroid hormone. We don't find significant differences in the gender (except IFG - predominantly in males).

Keywords: Graves - Basedow disease, diabetes, other changes in glycemic balance, adults

Introduction

Thyroid disorders are frequently associated with diabetes in clinical practice. In the case of diabetes mellitus (DM) type 1, because autoimmune etiology it is often associated with autoimmune thyroid disease (chronic autoimmune thyroiditis, Basedow-Graves disease). In the case of DM type 2 and other changes in glycemic balance, they usually appear secondary to excess of thyroid hormone or association is random.

Graves' disease is a type of autoimmune problem that causes the thyroid gland to produce too much thyroid hormone, which is called hyperthyroidism. Graves' disease is often the underlying cause of hyperthyroidism.

Autoimmune problems—of which there are many different types—develop when your immune system causes disease by attacking healthy tissues. Researchers do not completely understand what causes autoimmunity, although there seems to be a genetic connection, as cases of Graves' disease tend to run in families. For unknown reasons, like many autoimmune diseases, Graves' is also more likely to affect women than men.

The world incidence of the Graves-Basedow disease and the toxic multinodular goiter varies depending on the iodine intake. Compared to world regions with low iodine intake in the United States are more cases of Graves-Basedow disease and fewer cases of multinodular goiter (Yeung et al, 2005).

Graves-Basedow disease is the most common form of hyperthyroidism. Approximately 60-80% of cases of this disease are provided thyrotoxicosis. The annual incidence of the disease is 0.5 cases per 1,000 people, with a peak between 20-40 years. Multinodular toxic goiter (15-20% of thyrotoxicosis) occurs more frequently in areas deficient in iodine. Most people in the U.S. have sufficient iodine intake, the incidence of multinodular toxic goiter was lower than in iodine deficient regions of the world. Toxic adenoma is the cause of 3-5% of thyrotoxicosis (Lee et al, 2006).

Thyroid disorders have a peak incidence in the population aged 20-40 years. Toxic multinodular goiter occurs in subjects who have a long history of non-toxic goiter and, therefore, are usually present at the age of 50 years. Patients with toxic adenomas have this condition at a younger age than those with toxic multinodular goiter (Lee et al, 2006).

All thyroid diseases occur more frequently in women than in men. For example, in the case of autoimmune Graves - Basedow disease, the ratio M/F = 1/5-10. Toxic multinodular goiter and toxic adenomas occur more frequently in women than in men, with a ratio of 1/2-4 (Lee et al, 2006).

By contrast, hyperthyroidism is less common, with a female/male ratio of 9/1. Graves' disease is the most common and usually affects young adults. Toxic multinodular goiter usually occurs in older people (Wu, 2000).

Patients with diabetes have a high prevalence of thyroid disease compared with non-diabetic population (Wu, 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 (Wu, 2000).

A number of studies also indicate an increased prevalence of thyroid disease in patients with type 2 diabetes, hypothyroidism being the most common disorder encountered (Cooper et al, 2003). Thyroid disorders in the general population have a prevalence of 6.6%. In patients with diabetes, thyroid disease prevalence is between 10.8% and 13.4%, consisting of: clinical hypothyroidism (36%) sub clinical hypothyroidism (41%), hyperthyroidism (12%), and postpartum thyroiditis (11%) (Wu, 2000).

DM is associated with endocrine and systemic disease with autoimmune etiology of type: Graves-Basedow disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, pernicious anemia, myasthenia gravis, vitiligo, etc. (Cooper et al, 2003).

From people with DM type 1, $\approx$ 1-100 patients develop Graves' disease (De Block, 2000) and $\approx$ 1-20 patients are generally affected by hypothyroidism (De Block, 2000). The frequency of DM type 1 association with hyperthyroidism and hypothyroidism varies from 3.2% to 4.6% and from 0.7% to 4% (Radaideh et al, 2003)).

In the case of association between impaired glucose tolerance (IGT) and impaired fasting glucose tolerance (IFG) with thyroid disorder, they usually occur as a result of excess thyroid hormone. It was found that these associations are more common in women.

In a U.S. study it is shows that in patients with thyroid disorders, glucose intolerance was present in 38% of cases, and the incidence of clinical diabetes was $\approx$ 2-3% (Wartofski, 2000, Werner et al, 2000).

Type 2 diabetes is often associated with hyperthyroidism (Graves-Basedow disease and toxic multinodular goiter). Type 2 diabetes is present in 11% of patients with Graves-Basedow disease and in 5% of those with toxic multinodular goiter. Glucose intolerance is also frequently associated with hyperthyroidism, its prevalence is much higher compared to DM type 2 (72.3%). In the case of toxic multinodular goiter, incidence of glucose intolerance was significantly increased (85%), respectively 54% in the case of Graves-Basedow disease (Paul et al, 2004).

I:
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
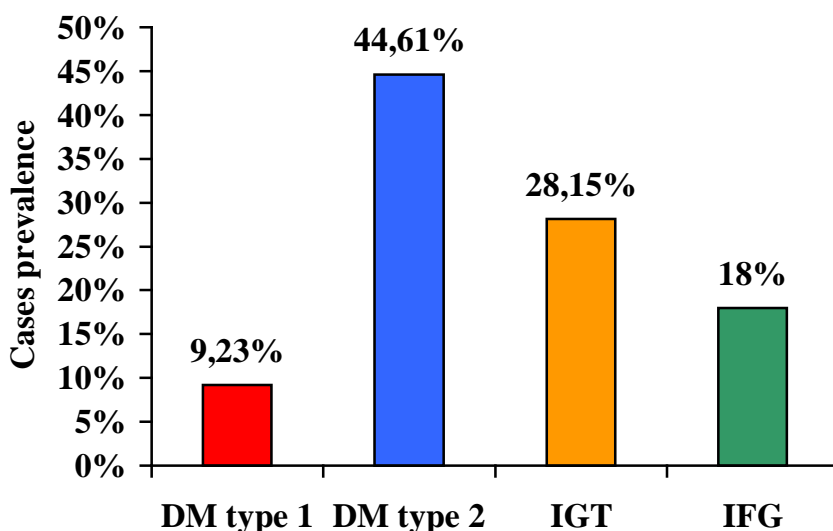- The group with IGT – 183
- The group with IFG – 117

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.

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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%)

The data obtained show that on the first place is type 2 diabetes (44.61%), followed by other types of changes in glycemic balance IGT (28.15%) and IFG (18%). DM type 1 met in the lowest proportion (9.23%). In the world, predominant is type 2 diabetes with a prevalence of 4.6%, while the prevalence of type 1 diabetes is 0.1%.

In Romania, 7% of diabetic patients presenting DM type 1, the remaining 93% were patients with type 2 diabetes.

Regarding the gender distribution, 588 people in the study were female (90.46%) and 62 males (9.54%), with a ratio F/M = 9.48/1 (Fig. 2). Patient selection corresponds with the literature, knowing that the incidence of thyroid disease is more common in women. In the case of DM type 1 group, gender distribution was net in favor of women being represented by 55 women (91.66%) and 5 men (8.34%), in ratio F/M = 11/1.

Around the world, a number of studies show a predominance of males in the incidence of type 1 diabetes in young adults. This male's predominance has been observed especially after puberty (Karvoven et al, 2003).

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

In the case of DM type 2 group, gender distribution was net in favor of women being represented by 252 women (86.9%) and 38 men (13.1%), in ratio F/M = 6.6 /1. Around the world, women predominate in some areas, while in other men.

In the DECODE study, the prevalence of type 2 diabetes was higher in women, while in the AusDiab study was higher in males (Tong et al, 2003).

In the case of IGT group, gender distribution was net in favor of women being represented by 173 women (94.5%) and 10 men (5.5%), in ratio F/M = 17.3/1.
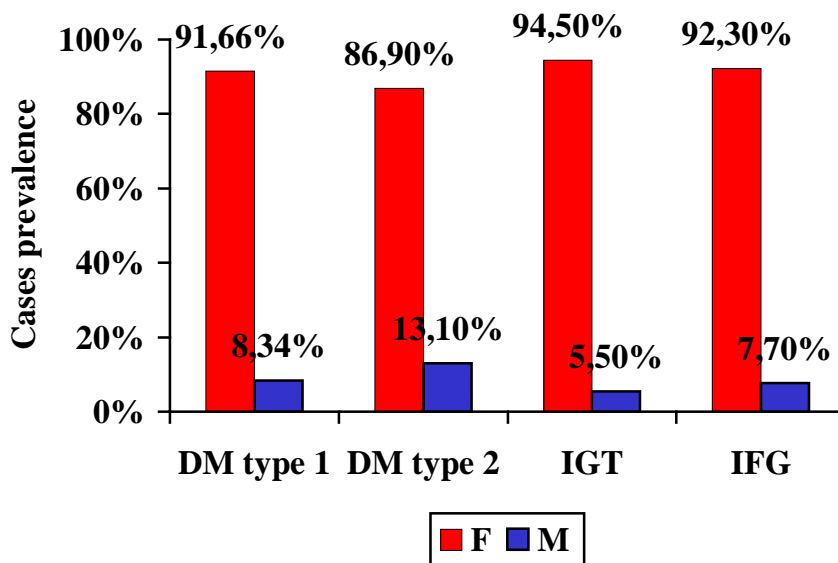

Figure 2. Distribution by gender of adults cases with changes in glycemic balance

In the case of IFG group, gender distribution was net in favor of women being represented by 108 women (92.3%) and 9 men (7.7%), in ratio F/M = 12/1.

In the DECODE study, IFG was more frequent in men than in women, whereas IGT was more frequent in women than in men (The DECODE study group, 2003).

In the DECODA study, IFG prevalence was higher in men than women in China and Japan, while in the Indians prevailed in women compared to men. IGT was more frequent in women than in men in Chinese and Japanese, this difference unnoticed in the Indians (The DECODA study group, 2003). In the study group, both IGT and IFG were more common in women, aspect consistent with increased prevalence of thyroid disease in women.

The mean age of the study group was 52 ± 12.46 years, median 52 years, with a minimum of 17 years and a maximum of 79 years.

The group of adults with type 1 diabetes included 60 people, young adults, adults and elderly, aged 18-72 years.

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

Parameters	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) (Karvoven 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 Graves - Basedow disease in the study group was 22.61% (21.76% F vs. 30.64% M, p = 0.11, X^2 = 2.53).

Graves - Basedow disease prevalence in the group with type 1 diabetes was 10% (9.09% F and 20% M, p = 0.38, X^2 = 0.75), 20.68% for type 2 diabetes (21.03% F and 18.42% M, p = 0.71, X^2 = 0.14), 23.49% for IGT (23.12% F and 30% M, p = 0.61 , X^2 = 0.25), and 32.47% for IFG (27.77% F and 88.88% M p = 0.00016, X^2 = 14.15).

Graves-Basedow disease is the most common cause of hyperthyroidism. A study in Minnesota estimated its incidence at 30 cases per 100,000 people per year (Yeung et al, 2005). Graves-Basedow disease is responsible for approximately 60-90% of cases of thyrotoxicosis in different regions of the world ((Yeung et al, 2005). In the UK Wickham study, the incidence is reported at 100-200 cases /100.000 persons / year (Yeung et al, 2005).

A number of studies show associations between thyroid disease with diabetes and other changes in glycemic balance. The most common thyroid disorders are autoimmune in the case of type 1 diabetes and 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 (Vondra et al, 2005). It increases with age and is strongly influenced by female sex and autoimmune diabetes (Vondra et al, 2005). Type 1 diabetes is commonly associated with endocrine and systemic disease with autoimmune etiology of type Graves-Basedow disease, autoimmune thyroiditis, Addison's disease, celiac disease, pernicious anemia, myasthenia gravis, vitiligo, etc. For people with type 1 diabetes ≈ 1/100 patients will develop Graves-Basedow disease while ≈ 1/20 patients are affected by autoimmune hypothyroidism.

Prina et al. (1994) found an increased prevalence of autoimmune thyroid disease association with type 1 diabetes (23.4%) than expected in the normal population (3-5%) and shows that younger age of diabetes onset

appears to be significantly associated with the development of thyroid disease (Prina et al, 2004).

The associations of different forms of change in glycemic balance with thyroid disease usually occur as a result of excess thyroid hormone. It was also found that these associations are more common in women.

Maxon et al. (1975) found the association of glucose intolerance and thyrotoxicosis. Glucose intolerance was detected in 32% cases, 43% of patients having a suggestive history of diabetes (Maxon et al, 1975).

Another study in India showed that autoimmune thyroid disease was diagnosed in 1.68 % of people with diabetes. DM was diagnosed in 2.3% of people with hypothyroidism and in 4.35 % of those with thyrotoxicosis (Sridhar et al, 2002).

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, the first being sub clinical hypothyroidism (4.8 %), followed by overt hypothyroidism (0.9 %), sub clinical hyperthyroidism (0.5%) and overt hyperthyroidism (0.5 %). Female patients with type 1 diabetes had the highest risk of developing thyroid disease (12.3 %), but all patients in 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 (Colin et al, 2004).

In the case of Graves-Basedow disease, the ratio F/B was 5/1 in the case of the group of diabetes type 1, 7.5/1 in the case of the group with type 2 diabetes mellitus 13.3 /1 in the case of the group with IGT and 3.75 / 1 for IFG. In The literature in regions where goiter is endemic, the prevalence rate in females can be 7/1, and in regions with endemic goiter, the ratio is lower (Wartofski, 2001).

The onset average age of thyroid disease is shown in the table below:

Table III. The onset average age of Graves – Basedow disease in the studied group

Parameters	Cases number	Average	Standard deviation	Median
DM type 1	6	33.33	13.57	34.5
DM type 2	60	50.96	10.97	48
IGT	43	45.04	10.88	49
IFG	38	39.52	10.96	41.5

The results correspond with the literature data, because Graves-Basedow disease usually occurs in young women (20-40 years), but can

occur at any age. Most affected are women aged 30-60 years (Wartofski, 2001).

Table IV. Graves – Basedow disease duration at adult studied group

Parameters	Cases number	Average	Standard deviation	Median	Minimum	Maximum
DM type 1	6	5.33	10.19	1.5	0	26
DM type 2	60	5.76	5.68	4	0	24
IGT	43	7.46	10.85	3	0	54
IFG	38	5.94	11.22	1.5	0	49

Table V. The interval of appearence between Graves – Basedow disease and differents changes in glycemic balance

Time interval	DM type 1	DM type 2	IGT	IFG
< 5 years	56.67%	67.93%	63.38%	66.66%
5 – 10 years	30%	15.17%	18.57%	14.52%
10 – 15 years	5%	8.27%	3.82%	5.98%
15 – 20 years	3.33%	2.75%	4.37%	5.98%
20 – 25 years	3.33%	3.10%	4.91%	3.42%
25 – 30 years	1.67%	1.38%	1.64%	0%
> 30 years	-	1.38%	3.27%	3.42%

Significant differences in the prevalence of Graves - Basedow disease were found only between type 1 diabetes and other changes in glycemic balance (10% vs. 23.49%, p = 0.023, X^2 = 5.11 for IGT, 10% vs. 32.47%, p = 0.001, X^2 = 10.73 for IFG) and between IGT and IFG (23.49% vs. 32.47%, p = 0.011, X^2 = 6.34).

Regarding the occurrence of Basedow-Graves disease in relation to diabetes and other changes in glycemic balance, in most cases the interval was between 0 – 10 years.

So, in the case of DM type 2, IGT and IFG, these appear after Graves – Basedow disease because of excess of thyroid hormones (in the case of surgery, because of replacement therapy with thyroid hormones). For DM type 1, this association is because of autoimmune origin.

The glycemic imbalance was mild in the case of DM type 2, IGT and IFG, most being treated with diet, and in the case of DM type 1 was severe, causing even ketoacidosis.

Conclusion

Graves - Basedow disease was mainly associated with other changes in glycemic balance (IGT and IFG) that occurred due to the presence of excess thyroid hormone

In 10% of cases were associated with type 1 diabetes due to autoimmune origin, part of the polyglandular autoimmune syndrome type III.

We don't obtained significant differences regarding the gender (except of IFG - predominantly in males)

Prevalence of Basedow – Graves's disease was increased in type 2 diabetes, IGT and IFG due to excess thyroid hormone causing mild glycemic imbalance (most had to be treated with diet).

So, if we have a patient with Graves – Basedow disease is better to investigate also the glucose metabolism through determination of glucose concentration annually.

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