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Type 2 diabetic patients with Graves' disease have more frequent and severe Graves' orbitopathy

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Abstract *Background and aims:* Due to the worldwide increasing prevalence of diabetes (DM), patients with both diabetes and Graves' disease (GD) have become more frequent. Sporadic reports indicate that Graves' orbitopathy (GO), a GD complication that affects orbital soft tissues, can be severe in DM patients. The relationship between these diseases is not well understood.

This study aims at evaluating the association of GD and GO with autoimmune and non-autoimmune diabetes (DM) and to assess diabetic features that influence GD and GO prevalence and severity.

Methods and results: This retrospective study evaluated GD, GO and DM association in 1211 consecutive GD patients (447 with GO and 77 with DM). A case-control study was carried out to evaluate DM relationship with GO severity by comparing at 1:2 ratio GO patients with or without DM. A strong association was found between GD and T1DM ($p = 0.01$) but not T2DM. Instead, the presence of GO was strongly associated with T2DM ($p = 0.01$). Moreover, GO was more frequently severe in GD patients with T2DM (11/30 or 36.6%) than in those without T2DM (1/60 or 1.7%, $p = 0.05$). T2DM was the strongest risk factor for severe GO (OR = 34.1 vs. 4.4 $p < 0.049$ in cigarette smokers). DM duration, obesity and vascular complications, but not metabolic control were significant determinants of GO severity.

Conclusions: GD is associated with T1DM but not with T2DM, probably because of the common autoimmune background. GO, in contrast, is more frequent and severe in T2DM, significantly associated with obesity, diabetes duration and diabetic vasculopathy but not metabolic control.

Introduction

Diabetes mellitus (DM) [1,2] has been reported to be a risk factor for Graves' orbitopathy (GO) [3]. GO is a manifestation of Graves' disease (GD) characterized by inflammation and expansion of retroocular soft tissues. Proptosis, malfunctioning of the extraocular muscles and optic nerve damage are the major clinical consequences that impair a patient's quality of life and may be sight-threatening [4–6]. GO severity is the result of a complex interaction between genetic (familiarity, gender, orbit characteristics) and non-genetic factors (smoking, radioiodine treatment, thyroid function) [6].

The mechanisms why diabetes can favor and worsen GO are unclear. One possibility involves the autoimmune background of the disorder. GD, GO and type I diabetes mellitus (T1DM) share an autoimmune nature and, in particular, can share susceptibility as well as involved loci

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of the HLA system [7,8]. Autoimmunity, however, has no role in the etiopathogenesis of type 2 diabetes mellitus (T2DM), which is approximately ten times more prevalent than T1DM [2]. Nevertheless, a number of T2DM cases with severe GO have been described. These cases might be the casual consequence of the high prevalence of T2DM in the population but may also have some unknown pathogenetic mechanism.

We evaluated the frequencies of GD and GO in patients with either autoimmune (T1DM) or non-autoimmune diabetes (T2DM) and evaluated in a case-control study which DM features are associated with more severe orbitopathy in matched groups of GD patients with or without diabetes.

Methods

We investigated two separate aspects of the association between GO and DM:

a) the prevalence of DM in a large series of patients with GD with or without GO; and
b) the severity of GO in GD patients with either T1DM or T2DM compared with matched GD/GO patients without diabetes.

These retrospective studies were carried out according to the guidelines of the ethics committee of our Hospital.

Patients

a) The prevalence of DM was calculated in 1211 patients with GD who received a medical examination and treatment at the Thyroid Clinic, Garibaldi Hospital Medical Center, Catania, Sicily, in the years 2002–2011. DM was diagnosed on the basis of glycosylated hemoglobin (HbA1c) $\geq$6.5% ($\geq$48 mmol/mol), fasting glycemia $\geq$126 mg/dl on two or more separate occasions and anti-diabetes treatment.

Diabetic patients were classified as having T1DM when diabetes was diagnosed before age 40 (with ketoacidosis in two cases) and in all patients with either C-peptide $<$0.2 nmol/l during fasting and positive autoantibodies (to GAD and IA2). Moreover, insulin treatment was required immediately or within a few months after diagnosis in all five T1DM patients. T2DM was diagnosed when diabetes never required insulin treatment or when insulin was added to oral treatment many years after diagnosis (6 cases). In all cases, after insulin addition, the fasting C-peptide was still higher than 0.6 nmol/l. Most of these patients were overweight (10/30) or obese (15/30), and in all cases, DM was diagnosed after age 45. All T1DM patients were treated with insulin, while T2DM patients were treated with either diet alone (6 cases) or with the addition of metformin (23 patients: 11 with only the biguanide, 7 combined with a sulfonylurea and 5 with bed-time insulin). One T2DM patient was treated with basal/bolus insulin injections after ten years of oral therapy.

In all 5 T1DM patients, DM onset preceded GD and GO occurrence. DM occurred before GD in 20/30 T2DM patients (average interval 6.6 years, range 2–24 years), was diagnosed at the same time in 6 cases, while in 4 patients, GD was diagnosed before T2DM.

b) The influence of DM on GO severity was evaluated with a retrospective case-control study carried out in GD patients with GO and DM. GO severity in these patients was compared to that observed in a matched control group of GD patients (1:2 ratio) having GO but not DM. Control patients were matched with the diabetic patients for the following factors that may influence GO: age ($\pm$5 years for T2DM and $\pm$10 years for T1DM), gender, body mass index (BMI), smoking habit, GO activity, thyroid function, presence of anti-TSH-receptor antibodies and GO duration.

The studied GD/GO diabetic series included all five patients with T1DM observed in the period 2002–2011 and 30/36 patients with T2DM observed in the same period. Six T2DM patients were not included in the study because one had maturity-onset diabetes of the young type 2 (MODY 2), one had severe diabetic retinopathy, one did not agree to the use of his clinical data, and three had incomplete anamnestic records and/or orbit data (lost at follow-up).

GO severity evaluation

GO severity and clinical activity stage were evaluated at the patient presentation in our Clinic by trained investigators according to the protocol of our Medical Center.

GO severity was evaluated according to the EuGoGo guidelines [9,10]. Lid fissure width was evaluated in millimeters by a router and proptosis with a Hertel exophthalmometer. Diplopia was classified according to the Gorman score [11]. A complete ophthalmological evaluation was carried out by an expert ophthalmologist. The GO was defined a) mild when features of GO have only a minor impact on daily life and patients had one or more of the following: minor lid retraction ($<$2 mm), mild soft tissue involvement, exophthalmos $<$3 mm above 21 (normal value for caucasian individuals in our experience), transient or no diplopia, corneal exposure responsive to lubrificants; b) moderate to severe when eye disease had sufficient impact on daily life with one or more of the following: lid retraction 2 mm or more, moderate or severe soft tissue involvement, exophthalmos 3 mm or more above 21, inconstant or constant diplopia and c) severe in case of dysthyroid optic neuropathy (DON) and/or corneal breakdown. Severe GO was graded as “clinical” when visual acuity was $<$0.6 pinhole acuity, and it was considered “subclinical” when visual acuity was between 0.6 and 0.9. To confirm the diagnosis of DON one or more of the following had to be present: apical crowding on computed

tomography scan of the orbit [12,13], disturbances in visual field examination compatible with DON, increased latency of visual evoked potential, and papilledema on fundoscopic examination. When the proptosis value between the two orbits was greater than 3 mm, the GO was defined as asymmetrical.

GO activity was staged according to the clinical activity score (CAS), as described by Mourits et al. [14].

Laboratory measurements

Serum hormones were measured by microparticle enzyme immunoassays (Abbott AxSYM-MEIA, Abbott Park, IL, USA) with inter-assay coefficients of variation of less than 10% over the analytical ranges of 1.7–46.0 pmol/l for FT3, 5.15–77.0 pmol/l for FT4 and 0.03–10.0 mU/L for TSH. The within-run and between-run precisions for the FT3, FT4 and TSH assays showed coefficients of variation <5%. TSH receptor antibodies (TRAb) were measured by a radioreceptor assay (RADIM, Italy). Plasma glucose, glycosylated hemoglobin (HbA1c) and C-peptide were evaluated by standard methods.

Statistical analysis

The SPSS 20.0 was used. The distribution of continuous variables was evaluated by the Shapiro–Wilk and Kolmogorov–Smirnov tests. Student's t-test or the Mann–Whitney U-test were used to evaluate continuous variables with normal or no-normal distributions. The Chi-square test was used to perform categorical data analysis. The Z-test was used to evaluate differences of the prevalence of GD, GO and/or DM in the studied patients and in the general population.

Results

Graves' disease and Graves' orbitopathy association with diabetes

In our series of 1211 patients with GD, diabetes was present in 77 cases (6.4%). This prevalence was higher than the prevalence of DM in Italy (4.9%) [2] ($p = 0.02$). When the diabetic patients were subdivided according to type 1 or type 2 DM, the calculated prevalence was 5.0% (60 cases/1211) for T2DM, not different from the prevalence of T2DM in the general population. In contrast, T1DM prevalence in GD patients (17 cases/1211 or 1.4%), was higher than the prevalence of T1DM in the general population (0.4%, range 0.3–0.6%; $p = 0.012$) [2]. These data indicate a significant association between GD and T1DM but not T2DM (Fig. 1A).

Among the 1211 GD patients, GO was present in 447 cases (39.4%), a percentage similar to that reported in other series [15]. When only the 77 patients affected by both GD and DM were considered, no difference was present between these patients (with GD and DM) and the 1134 GD patients without DM in terms of the known risk factors for GO (age, gender, smoking, ^{131}I-treatment).

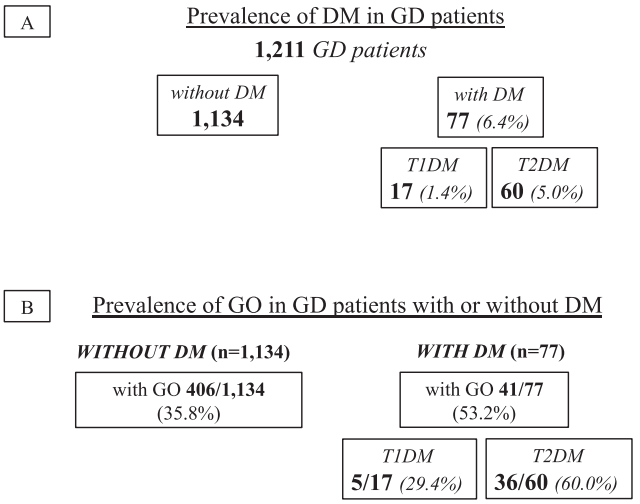

Figure 1 Indicates GD patients included in the study and subdivided according to the presence of GO and T1DM or T2DM. A) Association between GD and diabetes. B) Association between GO and diabetes.

However, GO was present in 41/77 GD cases with DM (53.2%), a percentage higher (although not significantly) than in GD patients without DM (406/1134 or 35.8%).

We than analyzed GO prevalence in GD patients according to the presence of either T1DM or T2DM. GO was present in 5 (29.4%) of the 17 patients with GD and T1DM, a value not different from the rate of GO in GD patients without DM (406/1,134, 35.8%, $p = 0.2$). In contrast, the prevalence of GO was significantly higher in GD patients with T2DM (36 cases/60 patients with GD and T2DM, or 60%) than in GD patients without DM ($p = 0.011$). These data indicate that T2DM, rather than T1DM, is frequently associated with the occurrence of orbitopathy in patients with GD (Fig. 1B).

Diabetes and GO severity in GD patients

A case-control study was carried out to evaluate GO severity in patients with GD and either T1DM or T2DM.

Type I diabetes

The characteristics of the five patients with T1DM and of the matched control group with GD and GO but without DM are shown in Table 1. The data indicate no significant difference for the examined parameters, including TRAb values and CAS. GO severity in the five T1DM patients was not different from that observed in the control group of GD patients with GO but without DM: proptosis, soft tissue involvement, motility impairment and diplopia were similar between the two groups (Table 2).

Type 2 diabetes

The characteristics of the 30 patients with GD, GO and T2DM were not significantly different relative to the matched controls (60 patients with GD and GO but without DM) (Table 1). Moreover, GO duration, CAS and TRAb were not different between the two groups.

Table 1 Clinical and laboratory characteristics of GD patients with GO and either T1DM or T2DM compared with matched GO/GD controls without DM.

	+ T1DM (n = 5)	− T1DM (n = 10)	P	+ T2DM (n = 30)	− T2DM (n = 60)	P
Age (years)	46.2 ± 8.2	54.7 ± 8.4	ns	62.7 ± 7.1	60.7 ± 8.2	ns
Sex (m/f)	2/3	4/6	ns	14/16	28/32	ns
Body mass index (BMI)	25.8 ± 2.3	26.9 ± 13.0	ns	31.5 ± 1.3	27.3 ± 2.9	0.014
Smoke (yes/no)	2/3	4/6	ns	8/22	16/44	ns
GD duration (months)	24 (1–70)	8 (1–96)	ns	16 (1–92)	6 (1–110)	ns
GO duration (months)	3 (1–10)	1.5 (1–8)	ns	5.5 (1–80)	1.8 (1–44)	ns
CAS	4.0 ± 0.7	4.0 ± 0.9	ns	4.4 ± 0.6	3.8 ± 0.5	ns
TSH (mU/L)	0.01 (0.0–0.06)	0.01 (0.0–0.03)	ns	0.01 (0.0–0.07)	0.01 (0.0–0.3)	ns
FT3 (pmol/l)	4.5 (3.7–7.7)	4.9 (1.6–23)	ns	6.3 (3.8–10.4)	5 (1.6–24)	ns
FT4 (pmol/l)	1.9 (1.4–3.7)	2.1 (1.2–4.2)	ns	2.4 (1.5–18.3)	1.9 (1.2–14.8)	ns
TRAb (U/L)	28.0 (11–141)	35.0 (18–304)	ns	48.0 (18–304)	45.0 (11–280)	ns
Glycemia (mg/dl)	217 ± 97.5	86.7 ± 8.3	<0.05	139 ± 31	85.7 ± 7.3	<0.05
HbA1c % (mmol/mol)	8.9 ± 2.4 (74 ± 19.9)	=		6.7 ± 1.1 (50 ± 8.2)	=	
Insulin treated (n)	5	=		6[a]	=	
OHA treated (n)	0	=		23	=	
Microvascular complications (n)	2/5	=		13/30	=	
Macrovascular complications (n)	1/5	=		8/30	=	

Data indicate mean values ± SD or median and ranges (in parentheses).
Normal values: TSH = 0.4–4.0 mU/L; FT3 = 2.3–4.2 pg/ml; FT4 = 8–18 pg/ml; C-Peptide = 1.07–3.51 ng/ml; HbA1c % = 4.25–5.85% (23–40 mmol/mol).
[a] 1 Patient insulin only; 5 patients insulin + metformin.

The prevalence of severe GO was much higher in T2DM patients (11/30, seven with clinical and four with subclinical DON). In the control group, only one patient had severe GO (1/60 = 1.7% vs. 36.6%, p = 0.042), and in this control patient, GO severity was not due to DON but to corneal breakdown (Table 2). All features of GO severity were significantly more frequent ($p < 0.05$) in T2DM patients than the control group: proptosis and soft tissue involvement were significantly increased, ocular motility more impaired and diplopia more frequent and severe. Moreover, GO was more frequently asymmetrical in T2DM patients.

In the seven T2DM patients with DON, extraocular muscle enlargement at the orbit apex (apex crowding) and severe visual field defects (evaluated at CT scan and campimetry, respectively) were present. Visual evoked potentials (VEPs) indicated that optical nerve conduction amplitude was reduced, and in 5/7 (71.4%), some degree of papilledema was observed at fundoscopy. In 2/7, a moderate and peripheral corneal damage was present. Among the four T2DM patients with subclinical DON, apex crowding at CT scan was observed in two. An additional difference between GD/GO patients with T2DM and controls without T2DM was that the onset of GO preceded the onset of hyperthyroidism (clinical and biochemical) in 4/30 T2DM patients (13.3%) vs. zero in the control group ($p < 0.05$).

Table 2 GO severity in GD patients with or without DM.

GO grading	+ T1DM	− T1DM	P
Mild n (%)	3/5 (60)	7/10 (70)	ns
Moderate to severe n (%)	2/5 (40)	3/10 (30)	ns
Severe n (%)	0	0	ns
	+ T2DM	− T2DM	P
Mild n (%)	8/30 (26.7)	35/60 (58.3)	<0.05
Moderate to severe n (%)	11/30 (36.6)	24/60 (40)	ns
Severe n (%)	11/30 (36.6)	1/60 (1.7)	<0.05
Clinical DON	5/30 (16.7)	0	<0.05
Clinical DON + C.B.	2/30 (6.6)	0	<0.05
Subclinical DON	4/30 (13.3)	0	<0.05
C.B.	0	1/60 (1.7)	<0.05

Data indicate number of cases and percentages (in parentheses).
GD = Graves' disease; GO = Graves' orbitopathy; DON = Dysthyroid optic neuropathy; C.B. = corneal breakdown; T1DM = Type 1 diabetes; T2DM = Type 2 diabetes.

In the 105 GD/GO patients studied (35 with and 70 without DM), we then evaluated whether DM was a risk factor for severe GO and diplopia compared with other potential or well-established risk factors, such as age (>60 y), gender (male), abnormal thyroid function (hyperthyroidism as indicated by serum FT3 >5.5 nM), GD duration and cigarette smoking [16]. At the chi-square analysis, only cigarette smoking and DM were significant predictors of severe GO (Table 3). Moreover, DM was a much stronger determinant of GO severity (OR = 31.6 vs. 4.4 for cigarette smoking; p = 0.001) but also the only significant predictor of diplopia (OR = 2.3; p = 0.03) (Table 3). GO severity significantly correlated with a T2DM duration longer than five years (OR = 4.9; p = 0.045) and the presence of vascular complications (including both micro- and macro-angiopathy, OR = 4.8; p = 0.048). GO severity was also correlated with patient overweight (BMI ≥ 26), but not with poor metabolic control of diabetes (p = 0.7) (Table 3).

Discussion

Our study in a cohort of 1211 unselected GD patients indicates that, compared to the general population, the prevalence of T1DM is significantly increased in GD

Table 3 Odds Ratio of different clinical and biochemical risk factors for GO severity (n = 105 GD/GO patients, 35 with and 70 without DM).

	n	Severe GO (n = 12)		Diplopia (n = 41)	
		OR (95% C.I.)	p	OR (95% C.I.)	p
Age (≥60 years)	55	1.3 (0.4–4.4)	0.8	0.8 (0.4–1.7)	0.7
Gender (M)	48	0.5 (0.2–1.9)	0.4	1.2 (0.6–2.6)	0.7
Hyperthyroidism (FT3 ≥ 5.5)	31	0.6 (0.3–1.1)	0.9	0.4 (0.2–1.2)	0.3
GD duration (≥6 months)	56	1.8 (0.4–7.6)	0.5	1.1 (0.4–2.8)	0.4
Smoking (yes)	30	4.4 (1.3–14.8)	0.01	1.5 (0.6–3.6)	0.5
DM (T1 and T2) (yes)	35	31.6 (3.8–258.1)	0.001	2.3 (1.0–5.3)	0.03
T2DM (yes)	30	34.1 (4.1–282.1)	0.001	3 (1.2–7.8)	0.014
T2DM duration (≥5 years)	12	4.9 (1.0–24.2)	0.045	2.3 (0.3–12.1)	0.4
Macro-vascular complic. (yes)	8	4.8 (1.0–25.1)	0.048	0.6 (0.1–2.4)	0.45
Micro-vascular complic. (yes)	13	4.8 (1.0–24.1)	0.049	0.6 (0.1–1.9)	0.5
HbA1c > 7% (>53 mmol/mol)	11	0.5 (0.01–2.7)	0.7	0.8 (0.3–2.1)	0.4
BMI (≥26)	24	1.8 (1.3–2.7)	0.007	0.8 (0.3–1.9)	0.6

OR = odds ratio, C.I. = confidence interval, BMI = body mass index (height/m^2).

patients. Moreover, among GD patients, those with T2DM more frequently had GO compared to GD patients without T2DM (60% vs. 35.8%, respectively, p = 0.011). The observation that DM is a risk factor for GO was already made by Kalmann and Mourits 15 years ago in a series of 462 GO patients in the Netherlands [3]. In their series, however, DM occurred in 3.1% of GO patients vs. 9.2% in our series. This difference may be due to the striking increase of GO patients with T2DM (1.4% in their 1999 paper vs. 8.1% in our series), reflecting the worldwide T2DM increase in the last two decades.

The increased association between T1DM, but not T2DM, and GD is expected because T1DM and GD share common genetic susceptibility, most likely determined by multiple genetic loci with HLA having the strongest effect. Both diseases are associated with the DR3-DQ2/DR4-DQS haplotype and participate in autoimmune polyendocrine syndrome type II (APS-II), which may also include adrenal insufficiency, autoimmune thyroiditis and more rare autoimmune disorders, such as vitiligo and hypogonadism [7,8]. In the five T1DM patients of our series, T1DM onset always preceded GD and GO onset. The reason why in APS each component disorder is present or why it may have a more precocious onset is unclear. Organ specific autoimmunity development most likely depends, on the basis of a common susceptibility, on other factors (genetic and environmental), including local lesions and precipitating events. When one disorder is present, however, an associated disorder occurs more frequently than in the general population, and this explains the T1DM and GD association.

The increased association between T2DM and GO occurrence and severity is more difficult to explain. Factors other than autoimmunity are likely to play a role. Possible mechanisms involve diabetic features that cause increased adipogenesis and inflammation, two processes typical of T2DM patients and both increased in orbital tissue of Graves' patients with GO. Sirtuin-1, a key regulatory component of macrophage influx into adipose tissue, is reduced in overweight subjects [17] and its decrease may favor the severity of GO in T2DM patients, that are obese for the large majority. Overweight, in our series, is significantly related with GO severity in T2DM patients.

Another possible mechanism involves insulin-resistance, overweight and compensatory hyperinsulinemia, also typical features of T2DM. Increased insulin can reduce IGF-1 binding proteins 1 and 2 thus increasing IGF-I bioavailability [18]. IGF-I receptors (IGF-IR), as well as TSH receptors (TSH-R), are overexpressed in orbital preadipocytes/fibroblasts and are involved in GO pathogenesis [19–22]. Their increased stimulation by increased IGF-I bioavailability can contribute to the expansion of the orbital content through both increased adipogenesis and overproduction of the extracellular matrix, especially hyaluronan. It has been recently demonstrated in vitro [23] that TSH-R and IGF1R activation cause additive effects in human orbital preadipocytes/fibroblasts via phosphatidylinositol 3-kinase (PI 3K) and the mammalian target of rapamycin (mTOR) pathways. Specific inhibitors of these signaling cascades have proven effective in vitro to decrease hyaluronan accumulation and adipogenesis [23] and should be tested as a non immunosuppressive treatment to reduce GO severity in T2DM patients.

Our study is not suitable for evaluating the role of DM therapy in the occurrence and worsening of GO in T2DM. Thiazolidinediones (TZDs) favor adipogenesis, expand retrobulbar fat and stimulate TSH receptor expression in orbital preadipocyte/fibroblasts [24] but in our series no T2DM patient was treated with TZDs [25]. Metformin increases glucagon-like peptide 1 (GLP-1) levels promoting adipocyte proliferation in the orbit [26]. GLP-I levels were not measured in our patients treated with metformin but the percentage of this treatment was similar in DM patients with either severe (8/11, 73%) or mild/moderate GO (15/19, 79%).

Finally the observation that both macrovascular complications and diabetes duration (two related features) [27,28] and also cigarette smoking [29,30] (a habit that negatively influences vascular function) are all associated with GO severity suggests that chronic vasculopathy may play a role in determining the severity of GO in patients with DM.

In conclusion, GO is more frequent and more severe in T2DM patients. This association requires special attention from diabetologists, endocrinologists and ophthalmologists. Many different mechanisms can potentially affect the orbit tissue and worsen GO in diabetic patients. Overweight/obesity, diabetes duration and micro- and macrovascular complications are the most relevant risk factors, while poor metabolic control and type of treatment do not appear to be relevant. Further studies are needed to better understand the underlying mechanisms and to discover better approaches to prevent and treat GO in diabetic patients.

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