Prevalence and Natural History of Graves' Orbitopathy in a Large Series of Patients With Newly Diagnosed Graves' Hyperthyroidism Seen at a Single Center

M. L. Tanda, E. Piantanida, L. Liparulo, G. Veronesi, A. Lai, L. Sassi, N. Pariani, D. Gallo, C. Azzolini, M. Ferrario, and L. Bartalena

Section of Endocrinology (M.L.T., E.P., L.L., A.L., L.S., N.P., D.G., L.B.) and Research Center in Epidemiology and Preventive Medicine (EPIMED) (G.V., M.F.), Department of Clinical and Experimental Medicine; and Department of Surgical and Morphological Sciences (C.A.), University of Insubria, 21100 Varese, Italy

Background: The prevalence and natural history of Graves' orbitopathy (GO) are poorly documented.

Methods: A large series of 346 patients with newly diagnosed and recent onset Graves' hyperthyroidism seen at a single (nontertiary referral) center over an 8-year period were enrolled in an observational prospective study and evaluated for GO activity and severity according to the EUGOGO (European Group on Graves' Orbitopathy) criteria. After excluding patients immediately treated for moderate-to-severe GO, patients undergoing total thyroidectomy or radioactive iodine treatment, and patients lost to follow-up, 237 patients were submitted to antithyroid drug (ATD) treatment, with ocular evaluation at 6, 12, and 18 months.

Results: Among the whole cohort, at presentation 255 (73.7%) had no ocular involvement, 70 (20.2%) had mild and inactive GO, 20 (5.8%) had moderate-to-severe and active GO, and 1 (0.3%) had sight-threatening GO with dysthyroid optic neuropathy. Of the 237 patients who completed the 18-month follow-up during or after ATD treatment, 194 (81.9%) had no GO at baseline. Progression to moderate-to-severe GO occurred in 5 (2.6%) of these patients. Of the 43 (18.1%) patients with mild and inactive GO at baseline, 1 (2.4%) progressed to moderate-to-severe GO, and 25 (58.1%) experienced complete remission.

Conclusions: Most patients with newly diagnosed Graves' disease have no ocular involvement. Moderate-to-severe and active GO or sight-threatening GO are rare at presentation and rarely develop during ATD treatment. Most patients (>80%) with no GO at baseline do not develop GO after an 18-month follow-up period. Remission of mild GO occurs in the majority of cases. **(*J Clin Endocrinol Metab* 98: 1443–1449, 2013)**

Graves' orbitopathy (GO), the main extrathyroidal manifestation of Graves' disease, is often disfiguring, impairs the quality of life of affected individuals, and causes great indirect and direct costs to health systems (1, 2). Its pathogenesis derives from a complex interplay of endogenous (nonmodifiable) and exogenous (modifiable) factors (3, 4). Preventive actions, such as quitting smoking or stable maintenance of euthyroidism, may to some extent prevent progression of mild forms of GO to more severe forms (5–7). Selenium is also useful for mild GO (8). Moderate-to-severe GO is best treated by immunosuppression when active, or

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Abbreviations: ATD, antithyroid drug; FT4, free thyroxine; FT3, free triiodothyronine; GO, Graves' orbitopathy; RAI, radioactive iodine; TRAb, TSH-receptor antibody; TSH, thyrotropin.

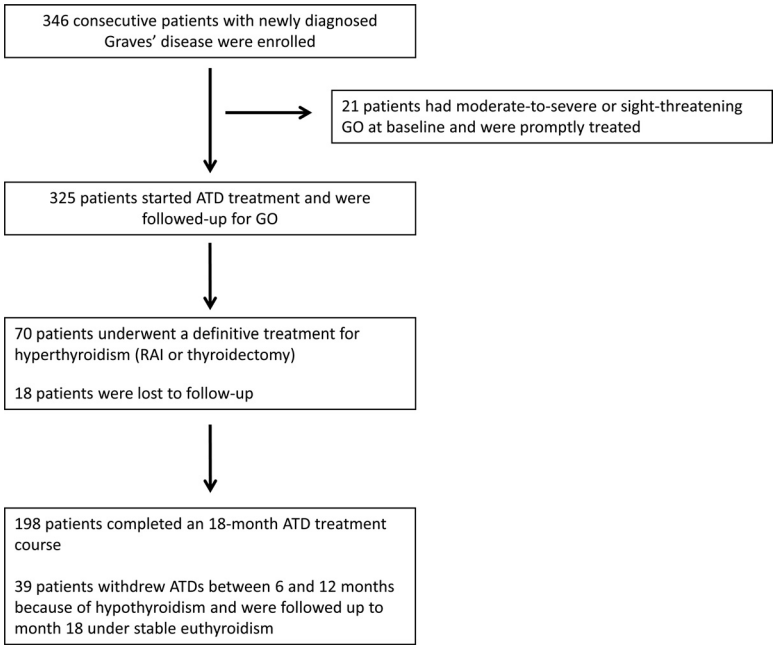

Figure 1. Enrollment and follow-up of the study patients.

surgery when inactive (9, 10). Many patients eventually require some kind of rehabilitative surgery (orbital decompression, squint surgery, eyelid surgery) when the disease course has ended (11, 12).

The prevalence and natural history of GO are poorly documented (13). The few existing studies evaluated either small series of patients or reported the experience of tertiary referral centers and thus may not reflect faithfully the prevalence and course of GO (14, 15). In addition, the prevalence of GO seems to be declining in the last decades (16), possibly in relation to changes in risk factors, such as a decrease in the prevalence of smokers (16, 17). The natural course of GO is not influenced by treating Graves' hyperthyroidism with either antithyroid drug (ATD) or surgical treatments, although restoration of euthyroidism may be associated with an amelioration of ocular involvement (18). At variance, radioactive iodine (RAI) treatment appears to be a disease-modifying treatment associated with progression or de novo appearance of GO in 15% to 35% of patients, particularly smokers (19–21). This untoward effect almost always can be prevented by steroid prophylaxis with low-dose oral prednisone concomitant with RAI treatment (22, 23).

The aim of this study was to evaluate in an observational prospective manner the occurrence and features of GO in a large series of consecutive patients with newly diagnosed Graves' hyperthyroidism seen at a single (nontertiary referral) center during an 8-year period. In addition, we evaluated the natural history of GO during an 18-month course of ATD treatment.

Materials and Methods

Patients

From October 2002 to October 2010, 346 consecutive patients with newly diagnosed hyperthyroidism attributable to Graves' disease were enrolled in a observational prospective study. The study was approved by the institutional ethical board, and patients gave their informed consent. The diagnosis of Graves' disease was based on standard criteria, including increased serum concentrations of free thyroxine (FT4) and triiodothyronine (FT3), undetectable serum thyrotropin (TSH), positive tests for TSH-receptor antibody (TRAb), diffuse goiter at palpation or ultrasonography, and homogeneous pertechnetate uptake at thyroid scan. ATD treatment with methimazole was instituted in all patients immediately after diagnosis. Of the initial cohort, 237 patients were followed up as long as 18 months while receiving methimazole treatment using the titration method (lowest methimazole dose that maintained euthyroidism) or during stable euthyroidism after cessation of ATD use between 6 and 12 months because of hypothyroidism (see Figure 1 and Results).

Assessment

Ocular involvement, including GO activity and severity, was defined as absent, mild, moderate-to-severe, active or inactive, according to criteria reported in the EUGOGO (European Group on Graves' Orbitopathy) consensus statement, including exophthalmometer readings, eyelid aperture, soft tissue changes, diplopia by Bahn and Gorman score, and clinical activity score (9). Patients with mild GO had only one of the following features: minor eyelid retraction (<2 mm), mild soft tissue changes, exophthalmos <3 mm above normal (in this case <20 mm), transient or no diplopia, or corneal exposure responsive to lubricants. Quality of life was not evaluated routinely by disease-specific questionnaires. Ocular imaging was not performed, except for patients with moderate-to-severe GO that was to be treated. Ocular evaluation was performed by an endocrinologist at baseline and at 6, 12, and 18 months during or after ATD treatment. Patients were referred to an ophthalmologist in the case of development or progression of GO. Serum FT4, FT3, TSH, and TRAb were measured at baseline and at 6, 12, and 18 months.

Assays

Serum FT4, FT3, and TSH were measured by immunoradiometric assays (DiaSorin S.p.A., Saluggia, Italy; normal values in our laboratory: 7.5–19 pg/mL, 2.3–5.7 pg/mL, 0.31–4.3 mU/L, respectively). TRAb was measured by radioreceptor assay (TRAK human; Brahms, Henningsdorf, Germany; normal value, <1 U/L).

Statistical analysis

Study subjects were divided into three groups based on the presence of GO at baseline: no GO (n = 255), mild and inactive

Table 1. Demographic Features of the Study Group at Enrollment

Feature	Figures
No. of patients	346
Women	266 (77%)
Men	80 (23%)
Age, y	45.7 ± 13.7
No. of smokers	122 (35%)
Positive family history for thyroid disorders	153 (44%)
Serum FT4 (pg/mL)	34.5 ± 15.0
Serum FT3 (pg/mL)	12.7 ± 7.9
Serum TRAb (U/L)	13.0 ± 11.3
Positive TRAb tests (>1 U/L)	98.9%

Data are mean ± SD. Serum TSH was undetectable in all patients at baseline.

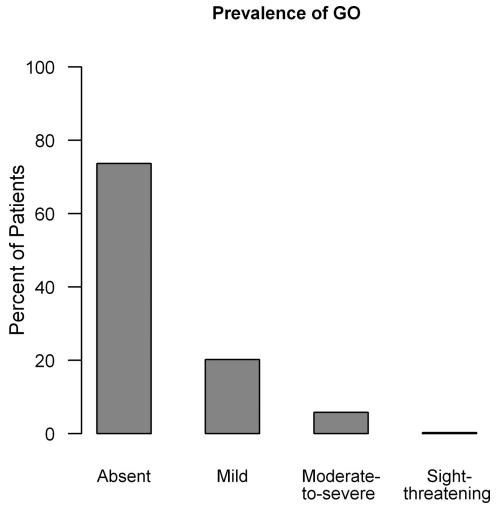

Figure 2. The absence or presence (and degree) of GO in the whole cohort of patients with Graves' hyperthyroidism at presentation. Of 346 patients, 255 had no signs or symptoms of GO, 70 had mild and inactive GO, 20 had moderate-to-severe and active GO, and 1 had sight-threatening GO.

GO (n = 70), or moderate-to-severe GO (n = 21). We compared main demographic and clinical features of the three groups through a standard ANOVA or χ^2 test, according to the nature of the feature. Pairwise differences between groups were also assessed when the overall null hypothesis was rejected. The association between age, smoking status, and TRAb with GO status at baseline was assessed by a multivariate generalized logistic model. The model included an interaction term between age and gender because a preliminary analysis showed a differential effect of age in the two gender groups. After patients with moderate-to-severe GO were excluded, 325 patients with no or mild GO at baseline were included in the follow-up analysis. By month 18 of treatment, 26 subjects developed GO (either mild or moderate-to-severe). To investigate whether baseline characteristics might predict disease progression, we considered a multivariate Cox survival model with age, gender, smoking status, and baseline TRAb as predictors. All analyses were done using the Statistical Analysis System (SAS) Software for Windows, version 9.2 (SAS Institute Inc, Cary, North Carolina).

Results

During an 8-year period (October 2002–October 2010), 346 consecutive patients with newly diagnosed hyperthyroidism caused by Graves' disease were referred to our Endocrine Unit. The demographic features of the patients are illustrated in Table 1. The large majority of patients were women, with a female-to-male ratio (F:M) of 3.3. The mean (± SD) age in the whole group was 45.7 ± 13.7 years (range, 15–84 years), 45% of patients were between 40 and 59 years of age. Among all patients, 122 (35.3%) were current smokers. Duration of symptoms of hyperthyroidism, as reported by patients, ranged from 1 to 14 months (median, 3 months).

At diagnosis, 255 patients (195 women and 60 men, 73.7%, F:M = 3.25) had no signs or symptoms of GO, 70 (55 women and 15 men, 20.2%, F:M = 3.66) had mild and inactive GO, 20 (15 women and 5 men, 5.8%, F:M = 3.20) had moderate-to-severe GO, 1 (0.3%) had sight-threatening GO (Figure 2). Patients with moderate-to-severe GO or sight-threatening GO were significantly older (53.7 ± 13.6 years) than were patients with mild GO (43.9 ± 12.2 years, $P < .004$) or no GO (45.6 ± 13.6 years, $P < .001$) (Table 2). The proportion of smokers was higher in patients with mild (48.6%) or moderate-to-severe or sight-threatening (47.6%) GO than in patients with no GO (30.6%, $P < .01$) (Table 2). The prevalence of smokers in the general population is approximately 30%. There were no differences in serum FT4 and FT3 concentrations at baseline among the three groups (Table 2). With respect to patients with no GO, serum TRAb levels were significantly higher in patients with mild GO ($P = .005$) or moderate-to-severe or sight-threatening GO ($P = .02$), with no significant differences between the latter two groups (Table 2). The multivariate generalized logistic analysis of the whole cohort showed a significant association between moderate-to-severe GO and smoking habits, serum TRAb levels, and age (in women, but not in men) (data not shown).

All patients were initially treated with methimazole to restore euthyroidism. Patients with moderate-to-severe or sight-threatening GO were promptly submitted to iv glucocorticoid treatment with or without orbital radiotherapy. Of the 325 patients with no or mild GO, within 6 months, 70 patients underwent a definitive treatment (RAI treatment or thyroidectomy) for reasons independent of GO, including poor control of hyperthyroidism, intolerance to thionamides, suspicion of malignancy, and patient's choice; 18 patients were lost to follow-up (Figure 1). The remaining 237 patients either completed an 18-month ATD course (n = 198) or withdrew ATD therapy between 6 and 12 months (n = 39) because of hypothyroidism and were then followed up to 18 months in a stable euthyroid state (Figure 1). At baseline, 194 (81.9%) of them had no GO, and 43 (18.1%)

Table 2. Features of Patients at Enrollment According to the Absence or Presence (and Degree) of GO

Feature	Absent GO	Mild and Inactive GO	Moderate-to-Severe GO	*P* Value
Number	255	70	21	
Age, y	45.6 ± 13.6	43.9 ± 12.2	53.7 ± 13.6	.01
Women	195 (76.5%)	55 (78.6%)	16 (76.2%)	.93
Men	60 (23.5%)	15 (21.4%)	5 (23.8%)	
Smokers	78 (30.6%)	34 (48.6%)	10 (47.6%)	.01
Serum FT4 (pg/mL)	34.2 ± 15.5	36.5 ± 13.0	32.1 ± 14.9	.38
Serum FT3 (pg/mL)	12.7 ± 8.3	12.8 ± 6.3	12.1 ± 8.1	.93
Serum TRAb (U/L)	11.8 ± 10.8	15.9 ± 11.6	17.1 ± 13.9	.01

Data are mean ± SD. Overall *P* value: F-test (ANOVA) for mean values and χ^2 test for proportions. Null hypothesis: the three groups do not differ on average in the considered features.

had mild and inactive GO. As illustrated in Figure 3A, among patients who initially had no GO, at the last visit 169 (87.1%) still had no GO, 20 (10.3%) had mild GO, 5 (2.6%) experienced moderate-to-severe and active GO, with soft tissue changes, intermittent to inconstant diplopia, and a clinical activity score of ≥3 (of 7). Mild GO was characterized by mild soft tissue changes and intermittent diplopia. Among those who initially had mild GO, at the last visit 25 (58.1%) had no GO, 17 (39.5%) still had mild and inactive GO, and 1 (2.4%) experienced moderate-to-severe and active GO (Figure 3B). Improvement in this group, as well as progression in both groups, occurred in most cases between 6 and 12 months. Patients whose eye disease progressed to moderate-to-severe and active GO during ATD treatment were treated with iv glucocorticoids, associated with orbital radiotherapy in some cases; one patient was submitted to orbital decompression because of contraindications to glucocorticoids and irradiation. Serum TRAb concentrations progressively decreased during ATD treatment (mean decrease, −9.4 U/L; 95% confidence interval [CI], −11.5, −7.4), although this trend was less pronounced in patients who experienced disease progression (mean, −8.2 U/L; 95% CI, −17.3, 0.6). Among patients with mild GO at baseline, serum TRAb levels were significantly lower in those whose GO improved than in those whose GO did not improve (11.1 ± 7.7 vs 18.1 ± 9.3 U/L, $P = .01$). Patients who experienced improvement were also younger than those who did not (42.9 ± 12.1 vs 51.4 ± 10.0 years, $P = .02$). Probably because of the low number of patients who experienced progression to mild or moderate-to-severe GO during ATD treatment, multivariate survival analysis failed to show any significant association between progression of GO and age, gender, smoking habits, or serum TRAb levels at baseline. Except for the 39 patients who experienced hypothyroidism and stopped ATD therapy, the remaining 198 patients had normal serum free thyroid hormone levels throughout the observation period. However, serum TSH levels were below 0.1 mU/L in 30%, 15%, and 12% of patients at 6, 12, 18 months, respectively. Conversely, serum TSH levels ≥5 mU/L were observed in 17%, 9%, and 6% of patients at control visits. These abnormalities did not have any impact on GO outcome.

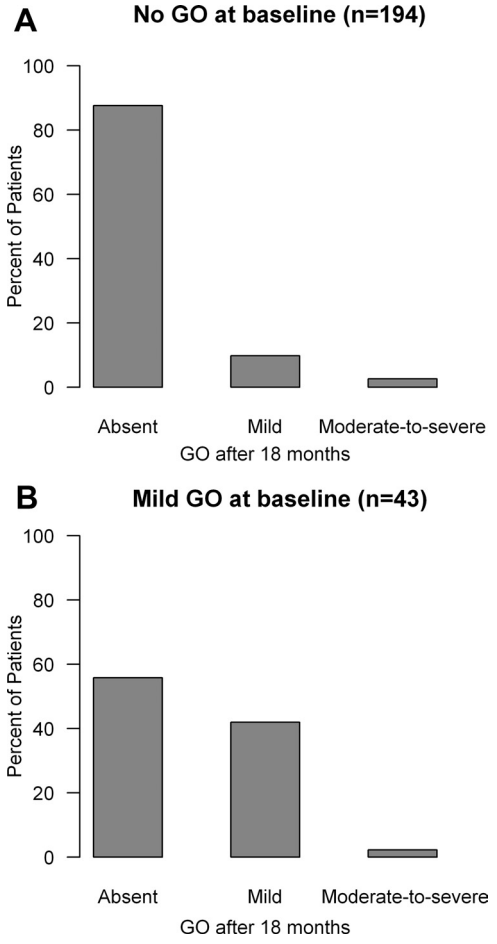

Figure 3. The course of GO in 237 patients with no or mild GO. Patients were either treated with methimazole for 18 months (n = 198) or followed up to 18 months in a stable euthyroid state after ceasing methimazole therapy between 6 and 12 months because of hypothyroidism (n = 39). Panel A, patients with no GO at presentation (n = 194). Panel B, patients with initially mild and inactive GO (n = 43).

Discussion

Data on the prevalence and natural history of GO are scarce and may be influenced by referral bias. It is com-

monly reported that about 50% of patients with Graves' disease have some degree of ocular involvement (1, 13, 16). In a questionnaire-based survey carried out in Europe about 15 years ago, many respondents believed that the incidence of GO had been decreasing in the previous decade (16). Likewise, a significant decline from 57% in 1960 to 35% in 1990 in the prevalence of GO among the first 100 patients consecutively presenting with a diagnosis of Graves' disease to a specialized thyroid-eye clinic was reported by Perros and Kendall-Taylor (24). In a review of 196 consecutive patients with Graves' disease referred to a single center, 81 (41%) were considered to have associated GO (15). A recent study from Sweden (an iodine sufficient country), based on the registry of a Swedish Multicenter Study, reported a prevalence of GO of approximately 20%, although criteria for the definition of eye disease were not defined (25). The severity of GO also seems to be declining. The incidence rate of moderate-to-severe GO in Denmark was reported to be 16.1/million per year (26.7/million per year in women, 5.4/million per year in men), with no variations after iodine fortification of salt and a relatively higher frequency in older groups (40–60 years) (17). In the current study, we enrolled a large series of almost 350 consecutive patients with newly diagnosed Graves' hyperthyroidism seen at our Endocrine Unit over an 8-year period. Our data clearly showed that GO, assessed using standardized criteria (9), currently is rare in Graves' disease at presentation, particularly in its more severe expressions. We are not a tertiary referral center. It might be argued that this might have introduced a referral bias because patients with more severe GO would be referred to a tertiary referral center. However, our Endocrine Unit is the only one in this area, and we believe that most, if not all, patients with newly diagnosed Graves' disease are referred to us. The large majority of patients (about 74%) had no ocular signs or symptoms, 20% had mild GO, and only 6% had moderate-to-severe GO. Sight-threatening GO caused by dysthyroid optic neuropathy was seen in only one patient at presentation. There was no difference in gender distribution among patients with no GO, mild GO, and moderate-to-severe GO. The prevalence of smokers was higher in patients with GO (irrespective of its severity) than in those without GO, confirming that smoking is a risk factor for the occurrence of GO (7). We cannot exclude that some of the patients classified as having no GO might have some degree of subclinical involvement because orbital imaging was not performed in those patients.

The natural history of GO is poorly documented. In a small series of 59 patients referred to a combined thyroid-eye clinic and followed up over a median period of 12 months, 13 (22%) experienced substantial improvement, 25 (42%) had slight improvement, 13 (22%) had unchanged ocular involvement, and 8 (14%) experienced progression to more severe forms (14). In our study, of the initial cohort of 346 patients, 237 either completed an 18-month ATD course or were followed up to 18 months in stable euthyroidism after ceasing ATD therapy between 6 and 12 months because of hypothyroidism. ATDs are generally considered to be neutral for the course of GO (26). Therefore, we believe that the course of GO in this cohort of patients faithfully reflects the natural history of the disease. Among the 194 patients who had no GO at baseline, the large majority had no GO (87.1%) or mild GO (10.3%) at the last visit. Progression to moderate-to-severe and active GO occurred in only 5 (2.6%) patients. Among the 43 patients who initially had mild GO, only 1 (2.4%) had disease progression to moderate-to-severe and active GO, whereas the majority (58%) showed a complete remission of eye manifestations. Overall, it would appear that GO, if not present in severe forms from the beginning, progresses in a minority of patients (about 5%) over time and is likely to remit in a large proportion of patients. These results expand our understanding of the natural history of GO in an unselected series of patients with Graves' disease.

How can these results be explained? It is well established that GO results from a complex interplay of endogenous (including incompletely understood genetic) factors and exogenous (environmental) factors. Among the latter, thyroid dysfunction per se and smoking habits play a major role. Control of both hyperthyroidism and hypothyroidism is beneficial for GO (27–29). Earlier diagnosis and correction of thyroid dysfunction is relevant in this regard. Likewise, a careful and stricter follow-up of patients receiving treatment can favor a stable maintenance of euthyroidism in most cases. Smoking is strongly associated with GO (30–34). Interestingly, the prevalence of smokers in the current series was only about 30%, much lower than that reported more than 20 years ago by our group (31). Thus, the decrease in smoking habits, as noted in the European survey by Weetman and Wiersinga (16), likely has an important role in the declining prevalence and severity of GO among patients with Graves' disease. This is in keeping with the results of a retrospective study indicating that refraining from smoking decreases the risk of exophthalmos and diplopia (35), and reinforces the concept that patients with Graves' disease should be urged to quit smoking as an important preventive action (7). All patients followed up prospectively were treated with ATDs. Whether ATD treatment, even prolonged for many years (36, 37), or early total thyroid ablation (38–40) is the optimal treatment for Graves' hyperthyroidism,

especially if GO is present at baseline, remains to be established (26, 41).

In conclusion, the results of this study in an unselected, large series of consecutive patients with newly diagnosed Graves' disease show that GO currently is a rare disease, particularly in its more severe expressions. Ocular manifestations remit in most patients with mild GO at presentation, whereas progression to more severe forms occurs in a few cases. The risk of developing GO is very low because most patients (>80%) with no GO at baseline do not have GO develop during an 18-month follow-up period. Apart from stable control of hyperthyroidism and the decrease in the proportion of smokers, the closer-than-in-the-past interaction between endocrinologists and ophthalmologists, as achieved by combined thyroid-eye clinics, likely plays a major role in this favorable outcome through more timely diagnosis and treatment of both thyroid dysfunction and initial ocular involvement (42). Medical management of moderate-to-severe GO is largely unsatisfactory. The rarity of moderate-to-severe GO, as shown by our study, underscores the difficulty of performing sufficiently powered randomized clinical trials of new drugs or different regimens of established treatment (43).

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Address all correspondence and requests for reprints to: Prof. Luigi Bartalena, University of Insubria, Department of Clinical and Experimental Medicine, Section of Endocrinology, Endocrine Unit, Ospedale di Circolo, Viale Borri, 57, 21100 Varese, Italy. E-mail: luigi.bartalena@uninsubria.it.

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