

High Prevalence of Radiological Vertebral Fractures in Patients With TSH-Secreting Pituitary Adenoma

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Background: Bone loss and high risk of fractures have been reported in patients with primary hyperthyroidism, whereas data on skeletal health in TSH-secreting adenoma (TSH-oma) are scant, and the risk of fractures in this specific clinical context has not been investigated so far. In this cross-sectional study, we aimed at evaluating for the first time, to our knowledge, the prevalence and determinants of radiological vertebral fractures (VFs) in patients with TSH-oma.

Methods: Twenty-two patients (10 males, 12 females; median age 47 years) with TSH-oma and 44 patients (20 males, 24 females; median age 49 years) with nonfunctioning pituitary adenoma (NFPA) were retrospectively evaluated for thoracic VFs using a morphometric approach on lateral chest X-ray routinely performed in the presurgical diagnostic workup.

Results: The prevalence of VFs was significantly higher in TSH-oma vs NFPA (59.1% vs 22.7%; $P = 0.003$), the difference being still significant (odds ratio, 10.5; $P = 0.005$) after correction for the size of pituitary adenomas and biochemical parameters. In TSH-oma, the prevalence of VFs was significantly associated with older age ($P = 0.007$) and higher serum free T4 values ($P = 0.02$). In 20 patients, data on presurgical medical therapies of TSH-oma were available. All patients not treated with somatostatin receptor ligands were fractured compared with 25% of those who were treated with these drugs ($P = 0.001$). No significant ($P = 0.25$) association between VFs and treatment with methimazole was found.

Conclusions: This study provides the first evidence, to our knowledge, that patients with TSH-oma may develop VFs in close relationship with severity of hyperthyroidism.

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Freeform/Key Words: hyperthyroidism, osteoporosis, somatostatin analogs, thyroid hormones, thyrotropin secreting adenoma, vertebral fractures

TSH-secreting adenoma (TSH-oma) is a rare disease accounting for 0.5% to 3% of all pituitary adenomas without sex differences [1–3]. Over the past decades, the incidence and prevalence of TSH-oma have increased due to improved awareness of disease and standardization of diagnostic approaches [2].

The inappropriate hypersecretion of TSH causes secondary hyperthyroidism, in which signs and symptoms are generally milder than those occurring in primary hyperthyroidism [4]. However, the diagnosis of disease is often delayed [4, 5] and patients with TSH-oma may

Abbreviations: BMD, bone mineral density; FT3, free T3; FT4, free T4; NFPA, nonfunctioning pituitary adenoma; PRL, prolactin; SRL, somatostatin receptor ligand; TSH-oma, TSH-secreting adenoma; VF, vertebral fracture.

be predisposed to develop chronic complications of thyroid hormone excess, such as cardiovascular events and skeletal fragility, as commonly observed in patients with primary hyperthyroidism [6, 7].

Thyroid hormones have physiological stimulatory effects on bone remodeling and bone mineralization, and normal euthyroid status during childhood and adolescence is required for acquisition of peak bone mass [8]. However, when thyroid hormones increase, bone remodeling is excessively stimulated with consequent bone loss, a decrease in bone mineral density (BMD), and an increase in vertebral and nonvertebral fracture risk [9–12]. Different from primary hyperthyroidism, only very few studies investigated the impact of secondary hyperthyroidism on skeletal end points, with data being limited to the evaluation of biochemical markers of bone turnover [13, 14], whereas the paucity of data on BMD and fracture risk is striking [15].

Vertebral fractures (VFs) are the most common complication of osteoporosis [16] and are associated with decreased survival [17] and impaired quality of life [18] in the general population. Because only about one-third of VFs are clinically recognized [16], the radiological and morphometric approach has emerged as the method of choice for evaluating the true prevalence and incidence of these fractures in population and clinical studies [19]. Different from other pituitary diseases [20], VFs have not been so far investigated in patients with TSH-oma.

In this retrospective study, we aimed at evaluating the prevalence and determinants of radiological thoracic VFs in patients with TSH-omas, using the routine X-rays performed before pituitary surgery.

1. Patients and Methods

A. Patients

Twenty-two patients (10 males, 12 females; median age 47 years, range: 27 to 68 years) with TSH-oma attending the Pituitary Unit of San Raffaele Hospital, Milan in the period between 2009 and 2016 were retrospectively and consecutively enrolled.

The inclusion criteria were (1) age older than 18 years, (2) biochemical and histological diagnosis of TSH-oma [21]; (3) availability of thoracic X-rays performed for anesthesiologic reasons before pituitary surgery (11 patients were excluded from the database during the data collection window due to the nonavailability of their thoracic X-ray images), and (4) full availability of information concerning the pituitary disease from the medical records. The exclusion criteria were (1) treatment with drugs potentially causing osteoporosis and fractures [22]; (2) treatment with bone-active drugs, except for calcium and vitamin D at the time of VF evaluation; and (3) history of thyroidectomy and/or neck radiotherapy [23].

The median duration of disease was 2 years (range, 1 to 23 years), as estimated by clinical history (*i.e.*, when the patient recalled appearance of signs and symptoms of the disease). Four patients had a mixed GH/TSH-secreting pituitary adenoma causing acromegaly co-existent with hyperthyroidism.

In 20 patients, data on presurgical medical therapies of TSH-oma were available. A history of somatostatin receptor ligand (SRL) and/or methimazole treatment was reported in 11 and 5 patients, respectively. Three of these latter patients were treated also with SRLs. In two of those patients, SRLs were stopped due to their inefficacy, whereas in one patient, methimazole was added to SRL to rapidly restore hormonal function in preparation for surgical intervention. The medical therapies were withdrawn 3 months before surgical treatment. Three male patients with TSH-oma were treated with testosterone for concomitant hypogonadism.

The control patients were retrospectively selected from a population of patients with nonfunctioning pituitary adenoma (NFPA) consecutively attending the Pituitary Unit in the same period as that of patients with TSH-oma. The criteria used for the selection were (1) diagnosis of NFPA, (2) comparable age and sex to the cases with a 2:1 ratio, and (3) availability of thoracic X-rays. Exclusion criteria were (1) history of hyperthyroidism; (2) treatment with drugs potentially causing osteoporosis and fractures [22]; (3) treatment with

bone-active drugs, except for calcium and vitamin D at the time of VF evaluation; and (4) history of thyroidectomy and/or neck radiotherapy [23].

The study was approved by the local ethical committee. It did not require a written consent of the patients due to the observational and retrospective nature of the study.

B. Biochemical Parameters

Fasting blood samples were collected for measurement of serum free T4 (FT4), free T3 (FT3), TSH, GH, IGF-I, ACTH, cortisol, prolactin (PRL), FSH, LH, total testosterone (in males), and estradiol (in females).

Serum TSH, FT4, FT3, and GH concentrations were measured by immunofluorometric assays (AIA-PACK; Tosoh Corp., Tokyo, Japan). Reference ranges for TSH, FT4, and FT3 were 0.25 to 4.5 μ UI/mL, 0.70 to 1.70 ng/dL, and 2.00 to 3.85 pg/mL, respectively. IGF-I was measured using an automated immunometric assay (Immulite 2000; Siemens Healthcare, Diagnostics Products Ltd, Llanberis, Wales), and normal ranges were age adjusted.

Serum ACTH, cortisol, PRL, LH, FSH, testosterone, and estradiol concentrations were analyzed using electrochemiluminescence immunoassay (ECLIA) (Cobas C 8000; Roche Diagnostics GMBH, Mannheim, Germany). Reference ranges for ACTH, cortisol, and PRL in males and females were 7.2 to 52 pg/mL, 48 to 195 ng/mL, 2.1 to 17.7 ng/mL, and 2.8 to 29.9 ng/mL, respectively. Reference ranges for testosterone, FSH, and LH in males were 2.5 to 8.4 ng/mL, 1.5 to 12.4 mU/mL, and 1.7 to 8.6 mU/mL, respectively. Reference ranges of FSH, LH, and estradiol in females were variable in relationship with phases of menstrual cycle and menopausal status.

C. VF Assessment

VFs were detected on lateral chest X-rays using a qualitative and quantitative evaluation of vertebral shape [24]. Using a translucent digitizer and a cursor, six points were marked on each vertebral body to describe vertebral shape. Anterior, middle, and posterior vertebral heights were measured, and height ratios (anterior/posterior, middle/posterior) were calculated for each vertebral body from T4 to T12. Measurements performed in two representative cases of TSH-oma and NFPA are reported in Supplemental Fig. 1. According to the method initially proposed by Genant *et al.* [24], fractures were defined as mild, moderate, and severe based on height ratio decreases of 20% to 25%, 25% to 40%, and >40%, respectively. Two experienced physicians (S.F., M.D.) blinded to the underlying diagnosis performed the analyses; the intraobserver and interobserver coefficients of variation were between 3% and 6% in relation to the severity (mild vs severe) of VFs.

D. Statistical Analyses

Data were presented as median and range, unless otherwise stated. The χ^2 test (or Fisher exact test when necessary) and Mann-Whitney nonparametric tests were used to compare categorical and quantitative data. Multivariate logistic regression analysis was performed to evaluate determinants of VFs in the study population. $P < 0.05$ was considered statistically significant.

2. Results

A. TSH-oma vs NFPA

Patients with TSH-oma showed higher serum TSH, FT4, FT3, IGF-I, testosterone, and LH values and a lower prevalence of macro-adenoma compared with patients with NFPA, without any significant differences in other clinical and biochemical parameters (Table 1).

The prevalence of total (59.1% vs 22.7%; $P = 0.003$) and multiple (31.8% vs 9.1%; $P = 0.03$) VFs was found to be significantly higher in TSH-oma compared with NFPA, without a significant difference (9.1% vs 6.8%; $P = 0.78$) in moderate/severe VFs between the two groups of patients (Fig. 1).

Table 1. Anthropometric, Clinical, and Biochemical Features of 22 Patients Affected by TSH-oma and 44 Patients With NFPA

Characteristic	TSH-oma (n = 22)	NFPA (n = 44)	P Value
Age, y	47 [27–68]	49 [29–68]	0.98
Sex, male/female, No.	10/12	20/24	1
Microadenoma/macroadenoma, No.	4/18	0/44	0.01
TSH, μ UI/mL	3.07 [1.36–19.79]	1.58 [0.19–6.83]	<0.001
FT4, ng/dL	2.18 [0.84–3.73]	0.99 [0.43–1.61]	<0.001
FT3, pg/mL	4.78 [2.10–8.70]	2.57 [1.55–4.39]	<0.001
IGF-I, μ g/L	203 [67–741]	120 [30–411]	0.02
GH, ng/mL	0.70 [0.10–14]	0.36 [0.07–9.7]	0.17
ACTH, pg/mL	19 [8–94]	22 [9–65]	0.48
Cortisol, ng/mL	133 [59–180]	121 [20–234]	0.75
PRL, ng/mL	9.0 [0.3–18.0]	12.0 [0.3–92.0]	0.13
LH, mU/mL	8.3 [1.7–39.6]	3.5 [0.1–35.0]	0.002
FSH, mU/mL	8.1 [1.0–88.8]	7.1 [0.3–75]	0.19
Estradiol, pg/mL ^a	48 [25–112]	53 [10–193]	0.91
Postmenopausal females, No. (%)	6 (50)	12 (50)	1
Testosterone, ng/mL	8.185 [1.30–13.80]	2.995 [0.025–6.25]	0.01
Male hypogonadism, No. (%)	3 (30)	9 (45)	0.43

Data are presented as median [range] unless otherwise indicated, and percentages and comparisons are performed by nonparametric tests.

^aLevels in premenopausal females.

The difference in VFs between TSH-oma and NFPA was still significant (odds ratio, 10.5; range, 2.5 to 53.3; $P = 0.005$) after correction for the size of pituitary adenomas, serum IGF-I, and LH values.

B. Determinants of VFs in TSH-oma

At the time of VF assessment, 17 patients (77.3%) had an overt hyperthyroidism and 5 patients (22.7%) had FT4 and FT3 values in the reference ranges (Fig. 2). In these latter patients, duration of normalization of thyroid function tests could not be ascertained based on available biochemical data during follow-up. TSH values were inappropriately normal in 17 patients (13 with overt hyperthyroidism and 4 with thyroid hormones in the reference ranges) and high in 5 patients (4 with overt hyperthyroidism, 1 with thyroid hormones in the reference ranges) (Fig. 2).

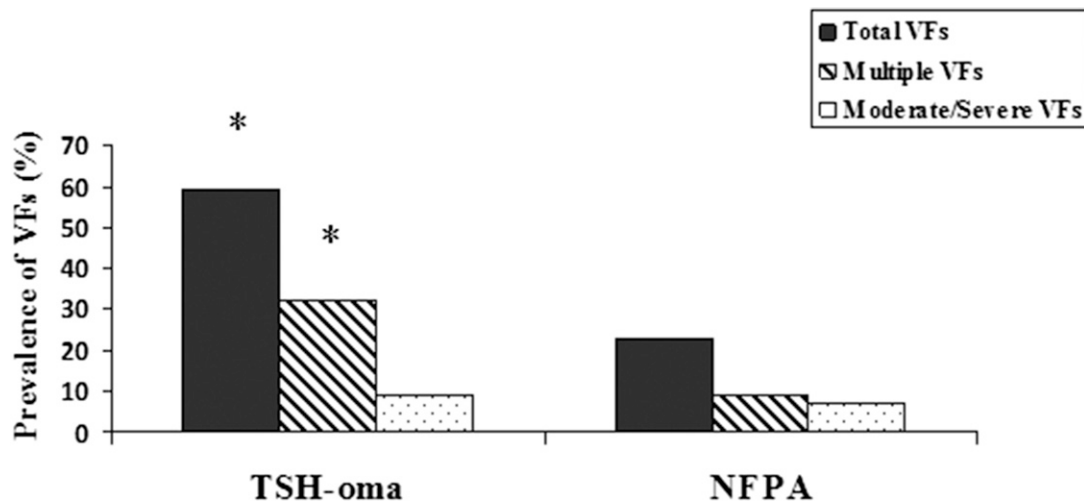


Figure 1. Prevalence of total, multiple, and moderate/severe VFs in 22 patients with TSH-oma compared with 44 patients with NFPA. * $P < 0.05$, TSH-oma vs NFPA.

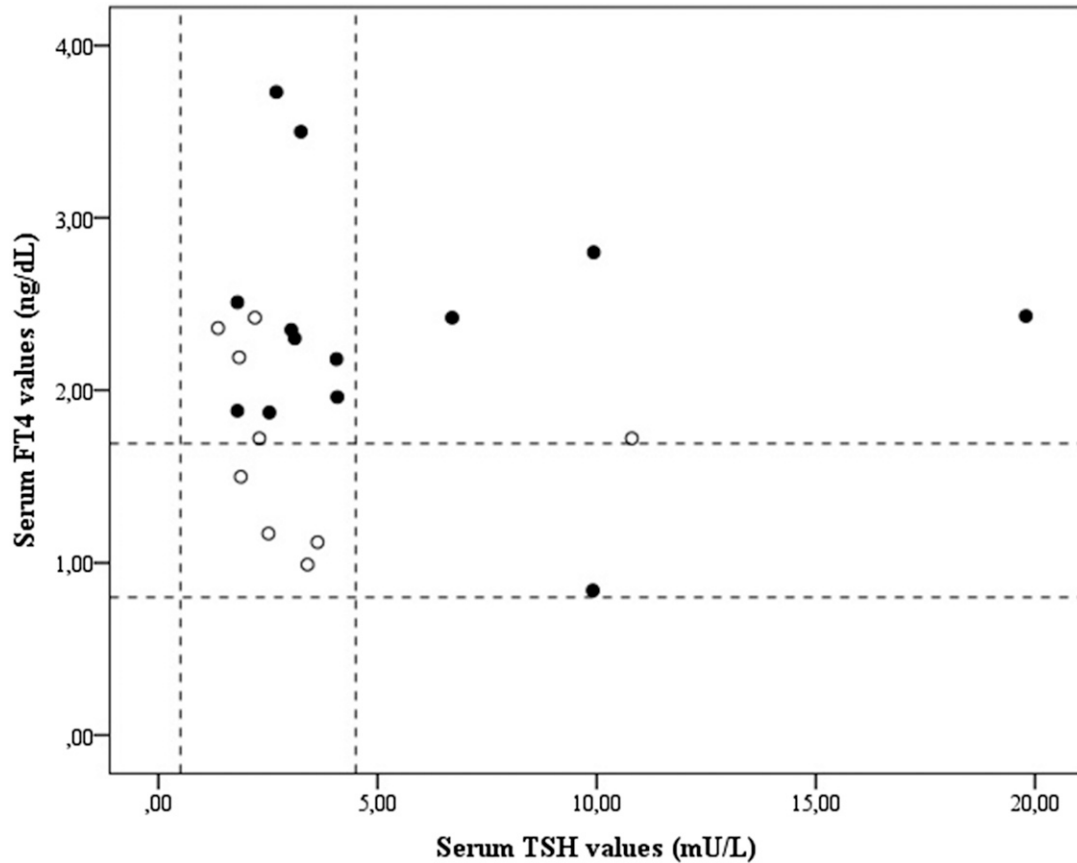


Figure 2. Distribution of serum TSH and FT4 values in patients with TSH-oma, stratified for presence (filled circle) or absence (open circle) of VFs. The dashed lines indicate the lowest and upper limits of the reference ranges for TSH and FT4.

Fractured patients with TSH-oma were significantly older than nonfractured patients ($P = 0.007$) and showed higher serum FT4 values ($P = 0.02$), without a significant association with duration of disease; serum TSH, FT3, PRL, and IGF-I values; gonadal status; and adrenal function compared with patients who did not fracture (Table 2). A nonsignificant trend toward a difference in menopausal status between fractured (five of seven females were in their menopausal period, 71%) and nonfractured patients (one of five was in postmenopause, 20%) was observed ($P = 0.24$). The prevalence of VFs was more frequent in patients with overt hyperthyroidism compared with those with thyroid hormones in the reference ranges (70.6% vs 20.1%; $P = 0.04$), whereas no significant difference was found when the patients were stratified for TSH values (normal TSH vs high TSH; 52.9% vs 80.0%; $P = 0.38$) (Fig. 2).

In 20 patients, data on presurgical medical therapies of TSH-oma were available. The prevalence of total and multiple VFs was significantly lower in patients treated with SRLs compared with those never treated with these drugs (Fig. 3). No significant association between VFs and treatment with methimazole was observed ($P = 0.25$). Two of four patients with GH-TSH cosecreting pituitary adenoma were shown to be fractured.

3. Discussion

This retrospective study reported for the first time, to our knowledge, a high prevalence of VFs in patients with TSH-oma in close relationship with the age of patients and severity of hyperthyroidism, as assessed by measurement of serum FT4 values. Moreover, presurgical treatment with SRLs was associated with a lower prevalence of VFs, whereas treatment with methimazole did not show any significant impact on fractures.

Table 2. Anthropometric, Clinical, and Biochemical Features of Nonfractured and Fractured Patients Affected by TSH-oma

Characteristic	No VFs (n = 9)	VFs (n = 13)	P Value
Age, y	37 [27–66]	56 [39–68]	0.007
Sex, male/female, No.	4/5	6/7	0.93
Microadenoma/macroadenoma, No.	3/6	1/12	0.12
TSH, μ UI/mL	2.30 [1.36–10.80]	3.25 [1.8–19.79]	0.14
FT4, ng/dL	1.50 [0.99–2.42]	2.35 [0.84–3.73]	0.02
FT3, pg/mL	4.03 [2.24–8.70]	5.30 [2.10–8.50]	0.23
IGF-I, μ g/L	207 [156–629]	203 [67–741]	0.35
GH, ng/mL	0.4 [0.1–8.1]	0.7 [0.1–14.0]	0.71
ACTH, pg/mL	18 [11–27]	29 [8–94]	0.18
Cortisol, ng/mL	121 [81–180]	136.5 [59–175]	0.99
PRL, ng/mL	7.6 [4.0–15.0]	9.4 [0.3–18.0]	0.28
LH, mU/mL	9.55 [5.7–22.6]	6.9 [1.7–39.6]	0.46
FSH, mU/mL	12.4 [4.4–41.0]	8.1 [1.0–88.8]	0.86
Estradiol, pg/mL ^a	43 [25–58]	71 [30–112]	0.94
Postmenopausal females, No. (%)	1 (25.0)	5 (71.4)	0.24
Testosterone, ng/mL	7.185 [5.47–8.90]	8.325 [1.3–13.8]	0.86
Male hypogonadism, No. (%)	1 (25.0)	2 (33.3)	0.78
SRL treatment, No. (%)	8 (100) ^b	3 (25.0) ^b	0.01
Methimazole treatment, No. (%)	3 (37.5) ^b	2 (16.7) ^b	0.35
Estimated duration of the disease, mo	45 [12–96]	24 [12–276]	0.97

Data are presented as median [range] unless otherwise indicated, and percentages and comparisons are performed by nonparametric tests.

^aLevels in premenopausal females.

^bThe percentages are calculated in 20 patients (8 without VFs and 12 with VFs) in whom the information on presurgical medical therapies was available.

The effects of thyroid hormones on bone metabolism are well established, ranging from impaired skeletal development in childhood hypothyroidism to an increased risk for osteoporosis in hyperthyroidism [25]. Bone loss with a high risk of vertebral and nonvertebral fractures has been widely reported in patients with primary hyperthyroidism [9–12, 26, 27]. In this clinical setting, bone damage is caused by the direct effects of thyroid hormones in excess on bone remodeling [8], although there is also evidence that low TSH values may play a role in driving fracture risk prevalently in euthyroid patients [28] or patients with primary hyperthyroidism [12]. In fact, several experimental and clinical studies have demonstrated that TSH has direct inhibitory effects on osteoclastogenesis and bone resorption [29–32], with concomitant stimulating effects on bone formation when the exposure to the hormone is intermittent [30, 31, 33, 34]. Based on these data, one could argue that primary and secondary hyperthyroidism may induce variable effects on bone in relationship to the different TSH values in the two diseases

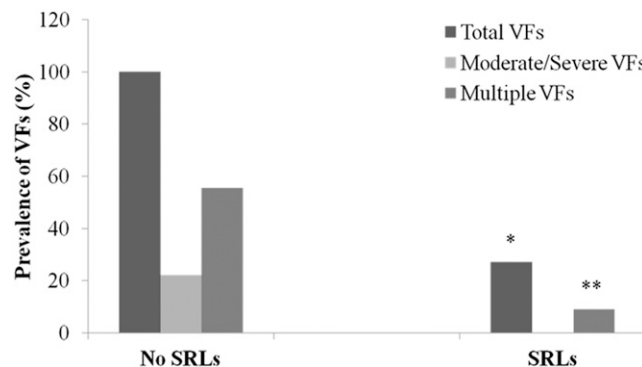


Figure 3. Prevalence of total, moderate/severe and multiple VFs in 20 patients with TSH-oma stratified for treatment with SRLs. * $P = 0.001$ vs no SRLs; ** $P = 0.02$ vs no SRLs.

(i.e., suppressed TSH values in primary hyperthyroidism and inappropriately either normal or high TSH values in secondary hyperthyroidism). Due to rarity of the disease, studies on bone involvement in TSH-oma are few and limited to evaluation of biochemical markers of bone turnover [13, 14]. Bone resorption was shown to be increased in patients with TSH-oma, with comparable values to those seen in primary hyperthyroidism and closely correlated to serum thyroid hormone levels [14]. Consistently, normalization of bone turnover was observed after treatment of TSH-oma [13]. However, in only one case report, data on fractures were reported [15].

To our knowledge, this is the first clinical study showing a high prevalence of VFs in patients with TSH-oma, in close relationship with age of patients and serum FT4 values but independently of TSH values and duration of disease. These findings suggest that VFs are an early complication of secondary hyperthyroidism, consistent with a published case report in which severe osteoporosis with multiple VFs was the clinical presentation of TSH-oma [15]. Our study proposes that VFs may develop early in the clinical history of TSH-oma in predisposed patients (more advanced age and possibly menopause, elevated thyroid hormones, no pretreatment with SRLs) as a direct consequence of hyperthyroidism. Actually, the potential osteoprotective action of TSH was overcome by the deleterious effects induced by thyroid hormones in excess. Indeed, normal or high TSH might not have exerted its full potential osteoprotective effects because the bone exposure was not intermittent. In fact, experimental studies showed that TSH may be protective for bone only when intermittently administered [30, 31, 33, 34], whereas persistently high TSH was shown to exert negative effects on osteoblastogenesis and bone formation [29]. On the other hand, we cannot exclude that in our patients affected by TSH-oma with thyroid hormones not increased over the reference range, normal or high TSH values may have exerted some protective effects on the skeleton. The prevalence of VFs in this limited group of patients appeared to be lower than that recently reported in primary subclinical hyperthyroidism induced by longstanding L-thyroxine therapy [12], in which low TSH values may have contributed to skeletal fragility.

Interestingly, >50% of our patients with TSH-oma showed VFs, a percentage that was comparable to that reported in other forms of secondary osteoporosis [35–37]. Noteworthy, the prevalence of VFs in TSH-oma was more than double compared with that in patients with NFPA, who are potentially predisposed to skeletal fragility and fractures due to coexistent hypopituitarism. Consistent with the hypothesis that NFPA may have been associated with hypopituitarism, our control patients had larger pituitary tumors and lower LH and IGF-I values compared with patients with TSH-oma, the latter finding being also influenced by the presence of four patients with acromegaly in the TSH-oma group. Furthermore, the difference in VFs between TSH-oma and NFPA remained significant even after correction for size of pituitary adenomas and serum IGF-I values, consistent with the concept that fractures in TSH-oma were caused by skeletal fragility secondary to thyroid hormone excess not significantly influenced by the potential negative effects on the skeleton of GH secretion abnormalities [38, 39]. Moreover, our control patients with NFPA showed lower testosterone values compared with patients with TSH-oma, despite the hypogonadism rate not being different between the two groups. Such an apparent discrepancy may reflect the stimulating effects of thyroid hormone in excess on sex hormone binding protein that may have induced higher total testosterone values in TSH-oma regardless of gonadal status [40]. Besides these pathophysiological considerations, it is relevant that the prevalence of VFs in TSH-oma was higher than NFPA, notwithstanding apparently better gonadal and pituitary status.

SRLs are used for the treatment of TSH-oma [2, 41, 42]. In our study, presurgical medical treatment with SRLs, but not that with methimazole, was associated with a lower prevalence of VFs. Moreover, it has to be noted that some patients treated with methimazole were “resistant” to SRLs. These findings were suggestive for a specific favorable effect of SRLs on skeletal health regardless of control of hyperthyroidism, similar to that observed in other settings for other clinical end points [43, 44]. However, the cross-sectional design of the study did not allow us to clarify the timing of VF development in relation to the start of medical therapies, and future prospective studies are needed to clarify whether SRLs may favorably influence fracture risk in patients with TSH-oma.

There are some limitations in our study to be acknowledged and discussed. The cross-sectional design did not allow us to determine the onset of VFs during the natural history of disease as well as the subsequent outcome of VF risk after treatment of TSH-oma. However, the results of cross-sectional analysis suggest that VFs may be an early complication of TSH-oma. Furthermore, we were not able to assess the possible protective role against VFs of long-term thyroid function normalization also due to the limited number of patients achieving this biochemical goal. Another limitation of our study was related to the mode of analysis of VFs, which was based only on evaluation of chest radiographs. This approach allowed us to identify only thoracic vertebral fractures, with likely underestimation of the true prevalence of VFs in this clinical context, although thoracic fractures are the most common osteoporotic fractures [45]. Third, our patients with TSH-oma were not investigated for bone metabolism and BMD. The lack of this information did not allow us to clarify whether the relationship between BMD and VFs in this clinical setting may be different from that already observed in patients with primary hyperthyroidism [12] or in other forms of osteoporosis associated with pituitary diseases [36, 37, 46–48].

Besides the aforementioned limitations, the results of this study may provide some practical insights into the management of TSH-oma. Diagnosis of TSH-oma is often delayed [4, 5] and patients are potentially predisposed to develop chronic complications of thyroid hormones excess, especially when their occurrence is early, as it seems for skeletal fragility. Based on the results of our study, the morphometric evaluation of VFs should be performed in all patients at diagnosis of TSH-oma, possibly accompanied by a measurement of BMD by dual energy X-ray absorptiometry (DXA) to have a comprehensive evaluation of skeletal health. This approach may be particularly indicated in older patients with TSH-oma who were shown to be more predisposed to fractures, similar to patients with primary hyperthyroidism [9]. The discovery of VFs in patients with TSH-oma may be clinically relevant for two reasons. First, the presence of multiple thoracic VFs in patients potentially affected by heart disease as a consequence of thyroid hormone excess may negatively affect the outcome of TSH-oma during the neurosurgical intervention [49]. In fact, thoracic VFs were associated with impairment of lung capacity in patients with chronic obstructive pulmonary disease and heart failure [50, 51]. Moreover, patients harboring VFs, even when asymptomatic, are at higher risk to develop further fractures even when the underlying disease is controlled or cured [52–54]. Therefore, fractured patients with TSH-oma should be followed up and/or treated for skeletal fragility regardless of the treatment of underlying disease. Accordingly, vertebral morphometry should be performed both at baseline and during follow-up in patients with TSH-oma. Finally, a relevant number of patients with TSH-oma are not cured by neurosurgery with a consequent relapse of hyperthyroidism [2, 42, 55–57]. Based on the preliminary results of our study, SRL treatment may be proposed in all those patients with active disease in place of methimazole for these apparent favorable effects on skeletal health.

In conclusion, to our knowledge, this is the first study showing a high prevalence of VFs in patients with TSH-oma, providing evidence that skeletal fragility may be a frequent complication of secondary hyperthyroidism.

Acknowledgments

Financial Support: This study was partially supported by Glucocorticoid Induced Osteoporosis Skeletal Endocrinology Group (GIOSEG).

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Disclosure Summary: G.M. received consultant fees from Novartis Farma and Ipsen. A.G. is a consultant for Ipsen, Novartis, and Pfizer. S.F., M.L., M.D., A.M.F., and P.M. have nothing to disclose.

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