Pituitary (2011) 14:299–306
DOI 10.1007/s11102-011-0293-4

High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas

Gherardo Mazziotti · Tatiana Mancini · Marilda Mormando · Ernesto De Menis · Antonio Bianchi · Mauro Doga · Teresa Porcelli · Pier Paolo Vescovi · Laura De Marinis · Andrea Giustina

Published online: 8 February 2011

Abstract Hyperprolactinemia may cause bone loss but data on fractures are scanty. The aim of this study was to evaluate the prevalence of vertebral fractures in women with prolactin (PRL)-secreting adenoma. In this cross-sectional study, 78 women (median age 45.5 years, range: 20–81) with PRL-secreting pituitary adenoma (66 with microadenoma and 12 with macroadenoma) and 156 control subjects, with normal PRL values and with comparable age to patients with hyperprolactinemia, were evaluated for vertebral fractures by a morphometric approach and for bone mineral density (BMD) by a dual-energy X-ray absorptiometry at lumbar spine. Vertebral fractures were shown in 25 patients with PRL-secreting adenoma (32.6%) and in 20 controls (12.8%, $P < 0.001$). Fractured patients were significantly older ($P < 0.001$) and had lower BMD T-score ($P < 0.001$), longer duration of disease ($P < 0.001$), higher serum PRL ($P = 0.004$) and lower serum IGF-I ($P < 0.001$) values as compared to patients who did not fracture. The prevalence of vertebral fractures was significantly ($P < 0.001$) higher in post-menopausal women with PRL-secreting adenoma as compared to pre-menopausal patients. Fractures occurred more frequently ($P = 0.01$) in patients with untreated hyperprolactinemia versus patients treated with cabergoline. Logistic regression analysis demonstrated that duration of disease maintained a significant correlation with vertebral fractures (odds ratio 1.16, C.I. 95% 1.02–1.33) even after correction for age, menopausal status, treatment with cabergoline, BMD, serum IGF-I and serum PRL values. Hyperprolactinemia is associated with high prevalence of radiological vertebral fractures in women with PRL-secreting adenoma.

Keywords Fracture · Prolactin · Bone metabolism · Pituitary adenoma · Osteoporosis

G. Mazziotti · M. Doga · T. Porcelli · A. Giustina
Endocrine Section, Department of Medical and Surgical Sciences, University of Brescia, Brescia, Italy

G. Mazziotti · P. P. Vescovi
Department of Medicine, "Carlo Poma" Hospital, Mantua, Italy

T. Mancini
Department of Internal Medicine and Medical Specialities, San Marino Hospital, San Marino, Italy

M. Mormando · A. Bianchi · L. De Marinis
Pituitary Unit, Division of Endocrinology, Catholic University of Rome, Rome, Italy

E. De Menis
Department of Medicine, General Hospital of Montebelluna, Treviso, Italy

A. Giustina (✉)
Department of Medical and Surgical Sciences, University of Brescia, c/o Endocrinology Service, Montichiari Hospital,Via Ciotti 154, 25018 Montichiari, Italy
e-mail: a.giustina@libero.it

Introduction

Prolactin (PRL) is a peptide hormone produced by the lactotrope cells in the anterior pituitary gland and is primarily associated with lactation. Hyperprolactinemia is a common finding in clinical practice and it may be caused by anterior pituitary or parasellar tumors or by anti-dopaminergic drugs [1, 2]. PRL-secreting adenomas are the most common type of secretory pituitary tumors accounting for about 40–60% of all pituitary adenomas [3, 4].

Sustained hyperprolactinemia causes oligoamenorrhea, infertility, and galactorrhea in women and decreased libido, erectile dysfunction, infertility and gynecomastia in men.

These clinical features mostly result from the negative effects of PRL on gonadotrophin-releasing hormone pulsatility which lead to inhibition of luteinizing hormone and follicle-stimulating hormone, and decreased secretion of estradiol and testosterone. PRL-induced hypogonadism is also considered the main mechanism leading to decreased bone mineral density (BMD) in patients with hyperprolactinemia [5–9]. However, there is also evidence that PRL excess may directly influence bone remodelling and bone metabolism [10–14].

An increase in bone resorption and low BMD were reported as frequent clinical features in men and women with PRL-secreting adenoma [15]. However, available data on the hard end-point of bone loss in hyperprolactinemia, i.e. fragility fractures, are scanty and based only on retrospective historical assessments of clinical fractures [16]. Current knowledge supports the clinical relevance of radiologically diagnosed vertebral fractures [17], but such evaluation of skeletal effects of hyperprolactinemia has never been performed.

In this cross-sectional study, we investigated the prevalence of radiological vertebral fractures in women with prolactinoma, in relation to BMD, gonadal function, duration of hyperprolactinemia, age of patients and age of onset of hyperprolactinemia.

Materials and methods

Subjects

We studied 78 women (median age 45.5 years, range: 20–81) with PRL-secreting pituitary adenoma (66 with microadenoma and 12 with macroadenoma) selected consecutively from out-patient endocrine clinics. The diagnosis of PRL-secreting adenoma was based on the detection of at least two samples with elevated PRL levels and neuroradiological evidence of pituitary tumor. The presumed disease duration was calculated from the time of appearance of symptoms probably related to the adenoma or hyperprolactinemia, such irregular menses, headache, galactorrhea and visual field defects. The median duration of disease was 5 years (range: 2–30). At the time of the study, 41 patients were on treatment with cabergoline whereas 37 had never been treated for hyperprolactinemia.

Thirthy-eight women were in pre-menopausal period (16 women with amenorrhea), whereas 40 women were in post-menopausal period at the time of the study (in 13 cases the diagnosis of hyperprolactinemia was made in pre-menopausal period, whereas in the remaining 27 women the diagnosis either coincided with menopause or was post-menopausal). Post-menopausal status was defined as cessation of menstrual cycles for more than 1 year. Eleven patients had secondary adrenal insufficiency, 8 patients had secondary hypothyroidism and 1 diabetes insipidus; all these patients were on adequate replacement therapy at the time of the study. Growth hormone deficiency was not tested by dynamic tests, but 9 patients with PRL-secreting macroadenomas had serum IGF-I values lower than the normal ranges for age.

One-hundred-fifty-six women without hyperprolactinemia (PRL values < 25 ng/ml), with comparable age to patients with hyperprolactinemia (Table 1), were enrolled as control group. These subjects performed anteroposterior and lateral spine X-ray examinations due to symptoms suggestive for a pathological involvement of thoracic-lumbar spine.

The inclusion criteria for patients and control subjects were: (1) no chronic treatment with drugs known to cause hyperprolactinemia; (2) no treatment with anti-osteoporotic drugs; (3) no chronic diseases (except for hyperprolactinemia in patients with prolactinoma) known to be associated with osteoporosis; (4) no previous treatment with drugs potentially causing osteoporosis and fragility fractures [18]; (5) no clinical history of recent significant trauma or prolonged immobilization.

All subjects gave their informed consent to the study which was approved by local Ethical Committees.

At study entry, all women were stratified for risk of osteoporosis and fragility fractures using a dedicated questionnaire which investigated the prevalence of cigarette smoking, alcohol intake, family history of fractures and time of menopause in postmenopausal women. Menopause before 45 years, parental history of hip or vertebral fractures, current cigarette smoking (more than 20 cigarette per day) and high alcohol consumption (3 or more units/daily) were considered as independent risk factors for osteoporosis and fragility fractures [19].

Measurement of BMD and quantitative morphometric assessment of vertebral fractures

BMD was measured at the lumbar spine by dual-energy X-ray absorptiometry (DXA) (QDR-1000 Hologic Inc., Waltham, MA, USA). These measurements were made at the time of the spine X-ray. BMD was expressed as T-score, comparing the results of each subject with those obtained in a sex-matched young population from USA. Osteopenia and osteoporosis were defined with T-score equal or below -1.0 standard deviation (SD) and equal or below -2.5 SD, respectively. Fractured vertebrae, assessed by the below reported methodology, were excluded from the lumbar BMD analysis [20].

For assessment of vertebral fractures, anteroposterior and lateral X-ray examinations of the thoracic and lumbar spine were performed. Vertebral fractures were identified initially by semiquantitative evaluation and then confirmed

Table 1 Clinical and demographical features of 78 women with prolactin (PRL)-secreting adenoma and 156 control subjects with normal PRL values

	PRL-secreting adenoma	Controls	*P* values
Cases	78	156	
Age (years)	45.5 (20–81)	46.0 (20–82)	0.94
Post/pre-menopausal women	40/38	77/79	0.78
Parental history of fractures	10 (12.8%)	31 (19.9%)	0.18
Current cigarette smoking	21 (26.9%)	46 (29.5%)	0.68
High alcohol consumption	2 (2.6%)	7 (4.5%)	0.47
Pre-menopausal amenorrhea	16 (20.5%)	0	<0.001
Early menopause	21 (26.9%)	15 (9.6%)	0.001
Serum PRL (ng/ml)	77 (4–1,490)	4.5 (3–16)	<0.001
Osteopenia	26 (33.3%)	35 (22.4%)	0.01
Osteporosis	18 (23.1%)	21 (13.5%)	
Size of adenomas (M/m)	12/66	–	
Duration of disease (years)	5 (2–30)	–	
Serum IGF-I values (ng/ml)	155 (24–324)	–	
Hypothyroidism	8 (10.3%)	–	
Glucocorticoid deficiency	11 (14.1%)	–	
Cabergoline therapy	41 (52.6%)	–	

M macroadenomas, *m* microadenomas, *IGF-I* insulin-like growth factor-1

by a quantitative morphometry assessment on centrally digitized images using a dedicated morphometry software (Spine-X Analyzer ICAM Diagnostics, Milan, Italy) [21]. In brief, using a translucent digitiser and a cursor, six points were marked on each vertebral body to describe vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Hm/Hp, Hp/Hp of the above vertebrae, Hp/Hp of the below vertebrae) were calculated for each vertebral body from T4 to L4; the fractures were defined mild, moderate and severe based on a height ratio decrease of 20–25%, 25–40% and more than 40%, respectively [21]. The morphometric analysis was performed by a single operator (G.M.) who was blinded to the identity of patients.

Statistical analysis

All data were expressed as the median and range. Un-paired data were compared using Mann–Whitney test. Frequencies were compared using Chi-square test with Fisher correction, when appropriate. A logistic regression model was used in the statistical analysis of risk factors for the occurrence of vertebral fractures. Statistical significance was assumed when *P* values were equal or less than 0.05.

Results

Thirty-four patients (43.6%) of patients with PRL-secreting adenomas had normal BMD T-score, whereas osteopenia was observed in 26 patients (33.3%) and osteoporosis in 18 patients (23.1%). The frequencies of osteopenia and osteoporosis were significantly higher in patients with prolactinomas as compared to control subjects (Table 1). Women with PRL-secreting adenoma also showed early menopause and amenorrhea more frequently as compared with control women, without any significant differences in parental history of fractures, cigarette smoking, high alcohol consumption (Table 1).

Vertebral fractures were shown in 25 patients with PRL-secreting adenoma (32.6%) and in 20 controls (12.8%; Chi-Square: 12.4, $P < 0.001$). In fractured patients with prolactinoma, 12 (15.4%) had single fractures and 13 (16.7%) two or more fractures. Fractures were mild in 11 patients (14.1%), moderate in 9 (11.5%) and severe in 5 (6.4%) fractured women with PRL-secreting adenoma. The frequencies of multiple fractures and severe fractures were not significantly different between fractured patients and controls.

Multivariate logistic regression analysis demonstrated that the correlation between PRL-secreting adenoma and vertebral fractures was independent of the effects of early menopause, amenorrhea and BMD (odds ratio: 2.9, C.I. 95% 1.3–6.6; $P = 0.008$).

Determinants of vertebral fractures in women with PRL-secreting adenoma

Fractured patients were older and had lower BMD T-score, longer duration of disease, higher serum PRL and lower serum IGF-I values as compared to patients who did not fracture, without any significant difference in frequency of

Table 2 Historical, clinical and biochemical data in fractured and non fractured patients with prolactin (PRL)-secreting adenoma

	Patients with PRL-secreting adenoma		
	Fractured	Not fractured	*P* values
Cases	25	53	
Age (years)	58 (38–81)	39 (20–61)	<0.001
Post/pre-menopausal women	22/3	18/35	<0.001
Parental history of fractures	4 (16.0%)	6 (11.3%)	0.56
Current cigarette smoking	8 (32.0%)	13 (26.5%)	0.49
High alcohol consumption	1 (4.0%)	1 (1.9%)	0.54
Pre-menopausal amenorrhea	2 (8.0%)	14 (26.4%)	0.06
Early menopause	10 (40.0%)	11 (20.8%)	0.07
Serum PRL (ng/ml)	104 (8–1,490)	60 (4–260)	0.004
BMD T-score (SD)	−1.9 (from −4.0 to −0.2)	−0.6 (from −3.0 to +2.4)	<0.001
Size of adenomas (M/m)	5/20	7/46	0.44
Duration of disease (years)	14 (2–30)	4 (2–25)	<0.001
Serum IGF-I values (ng/ml)	110 (24–267)	200 (78–324)	<0.001
Hypothyroidism	4 (16.0%)	4 (7.5%)	0.25
Glucocorticoid deficiency	4 (16.0%)	7 (13.2%)	0.74
Cabergoline therapy	8 (32.0%)	33 (62.3%)	0.01

M macroadenomas, *m* microadenomas, *IGF-I* insulin-like growth factor-1, *BMD* bone mineral density

early menopause, macroadenomas, adrenal insufficiency, hypothyroidism, parental history of fractures, cigarette smoking and high intake of alcohol (Table 2). Fractures occurred more frequently ($P = 0.01$) in patients with untreated hyperprolactinemia versus patients treated with cabergoline whose frequency of vertebral fractures was not significantly ($P = 0.4$) different as compared to control subjects (Fig. 1).

The prevalence of vertebral fractures was significantly ($P < 0.001$) higher in post-menopausal women with PRL-secreting adenoma as compared to pre-menopausal patients and post-menopausal control women (Fig. 2). In post-menopausal patients with PRL-secreting adenoma, vertebral fractures were significantly correlated with the duration of hyperprolactinemia (odds ratio: 1.16, C.I. 95% 1.04–1.30) but not with the age of onset of hyperprolactinemia (odds ratio: 0.72, C.I. 95% 0.4–3.6). In pre-menopausal women with PRL-secreting adenoma, the prevalence of vertebral fractures was not significantly ($P = 0.07$) different to that found in pre-menopausal control women (Fig. 2). Moreover, the prevalence of vertebral fractures in pre-menopausal patients was not significantly ($P = 0.37$) correlated with the presence of amenorrhea (Fig. 2). In pre-menopausal patients, the duration of hyperprolactinemia was significantly lower as compared to post-menopausal patients (4 years, range: 2–13 vs. 10 years, range: 2–30; $P < 0.001$).

In the whole group of hyperprolactinemic women, multivariate logistic regression analysis demonstrated that duration of disease maintained a significant correlation with vertebral fractures even after correction for age, treatment with cabergoline, BMD, serum IGF-I and serum PRL values (Table 3).

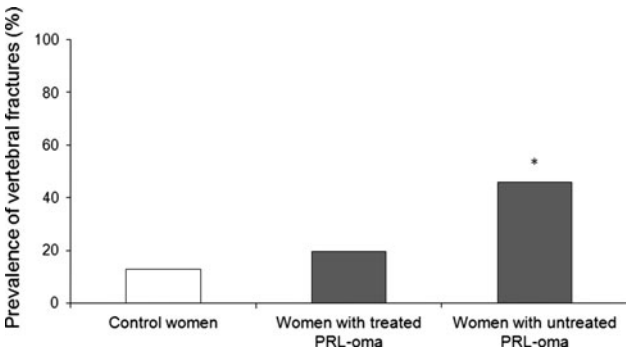

Fig. 1 Prevalence of radiological vertebral fractures in women with medically treated and untreated prolactin (PRL)-secreting adenomas as compared to control subjects with normal PRL values. *$P < 0.05$ treated patients versus untreated patients and control subjects

Discussion

This cross-sectional study shows that radiological vertebral fractures occur in about one-third of women with PRL-secreting pituitary adenomas. Vertebral fractures were significantly associated with duration of disease independently of the effects of hypopituitarism, age of patients, BMD, serum PRL levels and treatment with dopaminergic drugs.

Over the last 30 years, several studies have demonstrated that variable degrees of bone loss may occur in patients with hyperprolactinemia, with data being focused on BMD and clinical fractures [15, 16]. By contrast, this is the first study evaluating the prevalence of radiological vertebral fractures in patients with PRL-secreting adenomas. Vertebral fractures are the most common type of fragility fractures. Since vertebral fractures are often

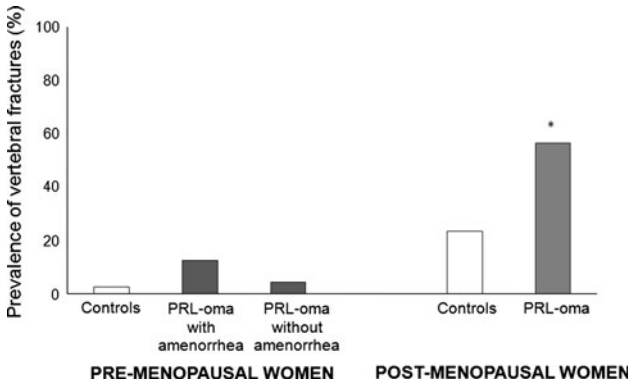

Fig. 2 Prevalence of radiological vertebral fractures in women with prolactin (PRL)-secreting adenomas (PRL-oma) as compared to control subjects with normal PRL values. $*P < 0.05$ post-menopausal women with PRL-oma versus pre-menopausal patients with PRL-oma and control women

Table 3 Results of logistic regression analysis using vertebral fractures as dependent variable and age, menopausal status, duration of disease, treatment with cabergoline, serum prolactin (PRL) and insulin-like growth factor-1 (IGF-I) values and bone mineral density (BMD) as covariates in 78 women with PRL-secreting adenoma

Covariates	Risk of vertebral fractures	
	Odds ratio (C.I. 95%)	*P* values
Age	1.1 (0.96–1.25)	0.17
Menopausal status	0.15 (0.09–2.63)	0.20
Duration of disease	1.16 (1.02–1.33)	0.03
Treatment with cabergoline	0.69 (0.08–5.88)	0.69
Serum PRL values	1.01 (0.99–1.02)	0.25
Serum IGF-I values	0.98 (0.97–0.99)	0.03
BMD T-score	0.52 (0.22–1.23)	0.13

asymptomatic and largely underdiagnosed based upon clinical records, the radiological and morphometric approach has emerged as the method of choice for evaluating the true prevalence of fractures in population studies [17, 21]. Vertebral fractures are clinically important since they impact the clinical outcome of patients with osteoporosis in term of development of new fractures and increase in morbility and mortality [22, 23].

A number of prevalence studies in post-menopausal osteoporosis have suggested that the risk of vertebral fractures is related to BMD [24]. Also in our patients, vertebral fractures were significantly correlated with BMD, but their prevalence was higher than that expected on the basis of T-score values. In fact, radiological vertebral fractures were found in more than one-third of the patients, even if a minority of our patients had osteoporosis. Indeed, it is well acknowledged that the relationship between BMD and risk of fracture is complex [25–27]. Fracture risk is related to bone strength that is dependent on two main physical/structural factors: quantity and quality. BMD reflects bone quantity but not bone quality which consists of structural and material properties [26–28]. Our finding is in agreement with the assumption that in secondary osteoporosis the fracture threshold is lower than in postmenopausal osteoporosis [29–32] and that PRL excess may impair significantly bone quality by direct effects on osteoblast function [11, 12, 33].

The traditional paradigm is that gonadal dysfunction is the most important factor leading to bone loss in hyperprolactinemic patients, since low BMD was already reported specifically in amenorrheic women [5–7] and hypogonadal men [8, 9]. However, there is also evidence that PRL may have sex hormones-independent effects on bone remodelling [11–14]. In fact, PRL receptor was demonstrated in osteoblasts and PRL was shown to decrease in vitro osteoblast proliferation with a secondary impairment of bone formation and mineralization [11, 12]. Moreover, PRL induced increase in RANKL/osteoprotegerin expression in osteoblasts leading to an increase in bone resorption [13, 14]. These experimental findings would suggest that hyperprolactinemia may cause bone loss regardless of hypogonadism. The results of our study seem to be consistent with this hypothesis, since we did not find difference in the prevalence of vertebral fractures between amenorrheic and eugonadal pre-menopausal females with PRL-secreting adenomas. Furthermore, we found higher prevalence of radiological vertebral fractures in post-menopausal women with hyperprolactinemia as compared with post-menopausal women with normal PRL values, in relationship with serum PRL values and mainly with duration of hyperprolactinemia.

Dopaminergic drugs are the primary therapy for prolactinomas [34] and in previous studies they led to a partial recovery of hyperprolactinemia-induced bone loss [35–38]. In our analysis, treated patients had significantly lower prevalence of vertebral fractures as compared to patients with untreated hyperprolactinemia. It is noteworthy that the prevalence of vertebral fractures in our women with treated hyperprolactinemia was not different to that observed in control women, suggesting that dopaminergic drugs may revert the risk of fractures in this clinical setting. However, the correlation between treatment of hyperprolactinemia and decrease of vertebral fractures was lost after correction for duration of disease, providing also suggestion that risk of fractures may remain high in patients with long-standing hyperprolactinemia independently of medical treatment. Alternatively, it may be hypothesized that at least in some patients (i.e. in postmenopausal women) biochemical target of PRL normalization was not pursued due to the lack of usual clinical end-points (infertility, amenorrhea).

Our study has some limitations. We did not assess properly the prevalence of growth hormone deficiency in

our patient. Indeed, some of our patients had hypopituitarism as effect of pituitary gland compression by PRL-secreting macroadenomas and growth hormone deficiency may have occurred in most of them. Indeed, growth hormone has important stimulatory effects on bone remodelling and bone mass [39] and growth hormone deficiency is associated with an increased risk of fragility fractures independently of other pituitary hormone abnormalities [40–43]. Serum IGF-I levels were lower in our fractured patients as compared to patients who did not fracture but this correlation did not seem to influence the correlation between vertebral fractures and duration of hyperprolactinemia (Table 3). Furthermore, the prevalence of vertebral fractures was not correlated with the size of pituitary adenomas which is an important determinant of the occurrence of growth hormone deficiency and hypopituitarism in this clinical setting. These findings would suggest that hyperprolactinemia may cause vertebral fractures independently of hypopituitarism. Another drawback of the study is related to its cross-sectional design, which does not allow to clarify the timing of hyperprolactinemia effects on fracture risk, as well as the existence of a biochemical target or a threshold PRL level associated with an increase of fracture risk. The correlation with the duration of disease would suggest that vertebral fractures may not be an early event, as observed in other forms of secondary osteoporosis [29, 42]. The cross-sectional design of the study did not permit to investigate the long-term skeletal impact of hyperprolactinemia developed during the attaining of peak of bone mass. Specifically, we cannot clarify whether a long-standing hyperprolactinemia in pre-menopausal period may have influenced in our patients the occurrence of vertebral fractures in post-menopausal period. Indeed, only prospective studies will allow to clarify this interesting aspect. Finally, due to the selected nature of our control population, which included subjects with signs and symptoms of spinal involvement, one can consider that the fracture risk in our hyperprolactinemic population could be even underestimated when eventually compared to an unselected general population.

Our study may have significant clinical implications. As in other forms of secondary osteoporosis, in patients with PRL-secreting adenoma the measurement of BMD may provide only few information on the fracture risk, since fractures may occur also in patients with osteopenia. Therefore, a spine X-ray with morphometric analysis should be performed for a complete skeletal assessment in patients with PRL-secreting adenomas with low BMD (either osteopenia or osteoporosis). The finding that post-menopausal women with hyperprolactinemia had high risk of vertebral fractures may lead to important changes in the management of prolactinomas in this clinical setting. In fact, the current guidelines recommend treatment of prolactinomas in post-menopausal women only if a macroadenoma is present or there are symptoms or signs due to mass effect or there is troublesome galactorrhea [44, 45]. However, based on our data, low BMD may be proposed as a further clinical criterion for treatment with dopamine agonist of prolactinomas in post-menopausal women. Furthermore, also withdrawal of dopaminergic agonists in women with prolactinomas entering physiological menopause has to be carefully evaluated [46–48], taking into consideration their skeletal status. The correlation between duration of hyperprolactinemia and vertebral fractures may encourage to perform a long-term skeletal monitoring in post-menopausal women with prolactinomas, even after starting dopaminergic drugs.

In conclusion, our data provide evidence that hyperprolactinemia may be a risk factor for morphometric vertebral fractures, which may significantly impact the long-term outcome of affected patients who should be considered candidates for careful monitoring of skeletal health.

Acknowledgments Study partially supported by MIUR, EULO and Centro Ricerca Sull'Osteoporosi-University of Brescia.

Conflict of interest All authors have no conflicts of interest.

References

1. Melmed S (2008) Update in pituitary disease. J Clin Endocrinol Metab 93:331–338
2. Mancini T, Casanueva FF, Giustina A (2008) Hyperprolactinemia and prolactinomas. Endocrinol Metab Clin North Am 37:67–99
3. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A (2006) High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 91:4769–4775
4. Fernandez A, Karavitaki N, Wass JA (2010) Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol 72:377–382
5. Klibanski A, Biller BM, Rosenthal DI, Schoenfeld DA, Saxe V (1988) Effects of prolactin and estrogen deficiency in amenorrheic bone loss. J Clin Endocrinol Metab 67:124–130
6. Biller BM, Baum HB, Rosenthal DI, Saxe VC, Charpie PM, Klibanski A (1992) Progressive trabecular osteopenia in women with hyperprolactinemic amenorrhea. J Clin Endocrinol Metab 75:692–697
7. Ciccarelli E, Savino L, Carlevatto V, Bertagna A, Isaia GC, Camanni F (1988) Vertebral bone density in non-amenorrhoeic hyperprolactinaemic women. Clin Endocrinol 28:1–6
8. Greenspan SL, Neer RM, Ridgway EC, Klibanski A (1986) Osteoporosis in men with hyperprolactinemic hypogonadism. Ann Intern Med 104:777–782
9. Greenspan SL, Oppenheim DS, Klibanski A (1989) Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. Ann Intern Med 110:526–531
10. Schlechte JA, Sherman B, Martin R (1983) Bone density in amenorrheic women with and without hyperprolactinemia. J Clin Endocrinol Metab 56:1120–1123

11. Coss D, Yang L, Kuo CB, Xu X, Luben RA, Walker AM (2000) Effects of prolactin on osteoblast alkaline phosphatase and bone formation in the developing rat. American J Physiol Endocrinol Metab 279:E1216–E1225
12. Seriwatanachai D, Krishnamra N, van Leeuwen JP (2009) Evidence for direct effects of prolactin on human osteoblasts: inhibition of cell growth and mineralization. J Cell Biochem 107:677–685
13. Seriwatanachai D, Charoenphandhu N, Suthiphongchai T, Krishnamra N (2008) Prolactin decreases the expression ratio of receptor activator of nuclear factor kappaB ligand/osteoprotegerin in human fetal osteoblast cells. Cell Biol Intern 32:1126–1135
14. Seriwatanachai D, Thongchote K, Charoenphandhu N, Pandaranandaka J, Tudpor K, Teerapornpuntakit J, Suthiphongchai T, Krishnamra N (2008) Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio. Bone 42:535–546
15. Shibli-Rahhal A, Schlechte J (2009) The effects of hyperprolactinemia on bone and fat. Pituitary 12:96–104
16. Vestergaard P, Jørgensen JO, Hagen C, Hoeck HC, Laurberg P, Rejnmark L, Brixen K, Weeke J, Andersen M, Conceicao FL, Nielsen TL, Mosekilde L (2002) Fracture risk is increased in patients with GH deficiency or untreated prolactinomas—a case-control study. Clin Endocrinol 56:159–167
17. Grigoryan M, Guermazi A, Roemer FW, Delmas PD, Genant HK (2003) Recognizing and reporting osteoporotic vertebral fractures. Eur Spine J 12:S104–S112
18. Mazziotti G, Canalis E, Giustina A (2010) Drug-induced osteoporosis: mechanisms and clinical implications. Am J Med 123:877–884
19. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A, Group NationalOsteoporosisGuideline (2008) Case finding for the management of osteoporosis with FRAX–assessment and intervention thresholds for the UK. Osteoporos Int 19:1395–1408
20. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 19:399–428
21. Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR (1996) Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in the osteoporosis. The study of osteoporotic fractures research group. J Bone Miner Res 11:984–996
22. Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, Segal M, Genant HK, Cummings SR (1998) The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 128:793–800
23. Jalava T, Sarna S, Pylkkänen L, Mawer B, Kanis JA, Selby P, Davies M, Adams J, Francis RM, Robinson J, McCloskey E (2003) Association between vertebral fracture and increased mortality in osteoporotic patients. J Bone Miner Res 18: 1254–1260
24. Lunt M, Felsenberg D, Reeve J, Benevolenskaya L, Cannata J, Dequeker J, Dodenhof C, Falch JA, Masaryk P, Pols HA, Poor G, Reid DM, Scheidt-Nave C, Weber K, Varlow J, Kanis JA, O'Neill TW, Silman AJ (1997) Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European centers: the EVOS Study. J Bone Miner Res 12:1883–1894
25. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JP, Pols HA (2004) Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 34:195–202
26. Cefalu CA (2004) Is bone mineral density predictive of fracture risk reduction? Curr Med Res Opin 20:341–349
27. Olesik A, Ott SM, Vedi S, Bravenboer N, Compston J, Lips P (2000) Bone structure in patients with low bone mineral density with or without vertebral fractures. J Bone Miner Res 15:1368–1375
28. Parfitt AM (1992) Implications of architecture for the pathogenesis and prevention of vertebral fracture. Bone 13:S41–S44
29. Mazziotti G, Angeli A, Bilezikian JP, Canalis E, Giustina A (2006) Glucocorticoid-induced osteoporosis: an update. Trends Endocrinol Metab 17:144–149
30. Vestergaard P (2007) Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. Osteoporos Int 18:427–444
31. Mancini T, Mazziotti G, Doga M, Carpinteri R, Simetovic N, Vescovi PP, Giustina A (2009) Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone 45:784–788
32. Mazziotti G, Porcelli T, Patelli I, Vescovi PP, Giustina A (2010) Serum TSH values and risk of vertebral fractures in euthyroid post-menopausal women with low bone mineral density. Bone 46:747–751
33. Canalis E, Giustina A, Bilezikian JP (2007) Mechanisms of anabolic therapies for osteoporosis. N Engl J Med 357:905–916
34. Molitch ME (2002) Medical management of prolactin-secreting pituitary adenomas. Pituitary 5:55–65
35. Klibanski A, Greenspan SL (1986) Increase in bone mass after treatment of hyperprolactinemic amenorrhea. N Engl J Med 315: 542–546
36. Schlechte J, el-Khoury G, Kathol M, Walkner L (1987) Forearm and vertebral bone mineral in treated and untreated hyperprolactinemic amenorrhea. J Clin Endocrinol Metab 64:1021–1026
37. Di Somma C, Colao A, Di Sarno A, Klain M, Landi ML, Facciolli G, Pivonello R, Panza N, Salvatore M, Lombardi G (1998) Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J Clin Endocrinol Metab 83:807–813
38. Colao A, Di Somma C, Loche S, Di Sarno A, Klain M, Pivonello R, Pietrosante M, Salvatore M, Lombardi G (2000) Prolactinomas in adolescents: persistent bone loss after 2 years of prolactin normalization. Clin Endocrinol 52:319–327
39. Giustina A, Mazziotti G, Canalis E (2008) Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev 29:535–559
40. Rosen T, Wilhelmsen L, Landin-Wilhelmsen K, Lappas G, Bengtsson BA (1997) Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. Eur J Endocrinol 137:240–245
41. Wuster C, Abs R, Bengtsson BA, Bennmarker H, Feldt-Rasmussen U, Hernberg-Stahl E, Monson JP, Westberg B, Wilton P, KIMS Study Group and the KIMS International Board. Pharmacia & Upjohn International Metabolic Database (2001) The influence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density. J Bone Miner Res 16:398–405
42. Mazziotti G, Bianchi A, Bonadonna S, Nuzzo M, Cimino V, Fusco A, De Marinis L, Giustina A (2006) Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. J Bone Miner Res 21:520–528
43. Mazziotti G, Bianchi A, Cimino V, Bonadonna S, Martini P, Fusco A, De Marinis L, Giustina A (2008) Effect of gonadal status on bone mineral density and radiological spinal deformities in adult patients with growth hormone deficiency. Pituitary 11:55–61
44. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A (2006) Guidelines of the pituitary society for the diagnosis and management of prolactinomas. Clin Endocrinol 65:265–273

45. Klibanski A (2010) Clinical practice. Prolactinomas. N Engl J Med 362:1219–1226
46. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G (2003) Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med 349:2023–2033
47. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM (2010) Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab 95:43–51
48. Molitch ME (2010) Pituitary gland: can prolactinomas be cured medically? Nat Rev Endocrinol 6:186–188