Endocr (2011) 39:288–293
DOI 10.1007/s12020-011-9462-5

ORIGINAL ARTICLE

Vertebral fractures in males with prolactinoma

Gherardo Mazziotti · Teresa Porcelli · Marilda Mormando · Ernesto De Menis · Antonio Bianchi · Carola Mejia · Tatiana Mancini · Laura De Marinis · Andrea Giustina

Received: 5 March 2011 / Accepted: 17 March 2011 / Published online: 10 April 2011

Abstract Data on osteoporotic fractures in hyperprolactinemia are limited. An increased prevalence of radiological vertebral fractures was recently observed in women with prolactin (PRL)-secreting adenoma, whereas it is unknown whether this observation may reflect a more general increased risk of fractures in this disease and whether the prevalence of fractures in males is affected by gonadal status. Thirty-two males (median age 47 years, range: 22–79) with PRL-secreting pituitary adenoma (10 with microadenoma and 22 with macroadenoma) and 64 control males, 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 12 patients with PRL-secreting adenoma (37.5%) and in 5 controls (7.8%, $P < 0.001$). Fractured patients had lower BMD T-score ($P = 0.007$) and longer duration of disease ($P < 0.001$) as compared to patients who did not fracture. Fractures occurred more frequently ($P = 0.03$) in patients with untreated hyperprolactinemia versus patients treated with cabergoline whose frequency of vertebral fractures was still higher than control subjects. The prevalence of vertebral fractures was not significantly different between eugonadal and hypogonadal patients (33.3% vs. 38.5%; $P = 0.8$). Moreover, no significant ($P = 0.4$) difference in serum testosterone values was found between fractured and not fractured males. Hyperprolactinemia is associated with high prevalence of radiological vertebral fractures in men with PRL-secreting adenoma. These findings would also suggest that PRL excess may produce negative skeletal effects independently of hypogonadism.

Keywords Fracture · Hyperprolactinemia · Bone metabolism · Pituitary adenoma · Male osteoporosis · Hypogonadism

G. Mazziotti · T. Porcelli · C. Mejia · A. Giustina
Department of Medical and Surgical Sciences, University of Brescia, Brescia, Italy

G. Mazziotti (✉)
Department of Medicine, "Carlo Poma" Hospital, 46100 Mantua, Italy
e-mail: gherardo.mazziotti@aopoma.it

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

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

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

Introduction

Prolactin (PRL)-secreting adenomas are the most common type of secreting pituitary tumors accounting for about 40–60% of all pituitary adenomas [1–3]. In men, sustained hyperprolactinemia causes decreased libido, erectile dysfunction, infertility and gynecomastia [3]. These clinical features result from the negative effects of PRL on gonadal function. PRL-induced hypogonadism is also considered the main mechanism causing bone loss in patients with hyperprolactinemia [4, 5]. An increase in bone resorption with low bone mineral density (BMD) has been shown to occur frequently in hypogonadal males and females with

hyperprolactinemia [6]. Data on the hard end-point of bone loss in hyperprolactinemia, i.e., fragility fractures, are scanty and focused on women with prolactinoma [7, 8], whereas it is still unknown whether there may be a more general increased risk of osteoporotic fractures in this clinical setting.

In this cross-sectional study it was evaluated the prevalence of radiological vertebral fractures, identified as deformities of vertebral bodies by a quantitative morphometric analysis, in a cohort of eugonadal and hypogonadal males with prolactinoma. In this unselected population, which cannot be defined as a whole at high risk of osteoporosis, the authors aimed at investigating whether the prevalence and degree of vertebral fractures were increased with respect to a control population and eventually related to the age, BMD, coexistent hypogonadism and persistent hyperprolactinemia.

Materials and methods

Subjects

The authors studied 32 males (median age 47 years, range: 22–79) with PRL-secreting pituitary adenoma (10 with microadenoma and 22 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 headache, visual field defects, impairment of libido and erectile dysfunction. The median duration of disease was 4 years (range: 1–20). At the time of the study, 23 patients were on treatment with cabergoline whereas 9 had never been treated for hyperprolactinemia.

Twenty-five patients had hypogonadism, as assessed by total serum testosterone concentrations below normal limits in presence of erectile dysfunction; at the time of study, 9 hypogonadal males were on long-term replacement treatment with testosterone. Twenty-one patients had secondary adrenal insufficiency, 19 patients had secondary hypothyroidism and 2 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 10 patients with PRL-secreting macroadenomas had serum IGF-I values lower than the normal range for age; these patients were not replaced with growth hormone due to the presence of adenoma.

Sixty-four males without hyperprolactinemia (PRL values <15 ng/ml), with comparable age to patients with hyperprolactinemia (Table 1) were enrolled as control group. These subjects attended out-patient bone clinics and 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 [9]; (5) no clinical history of recent significant trauma or prolonged immobilization.

At study entry, all men 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. Parental history of hip or vertebral fractures, current cigarette smoking (more than 20 cigarettes per day) and high-alcohol consumption (3 or more units/daily) were considered as independent risk factors for osteoporosis and fragility fractures [10].

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

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 [11].

For assessment of vertebral fractures, antero-posterior and lateral X-ray examinations of the thoracic and lumbar spine were performed. Vertebral fractures were identified initially by semiquantitative evaluation and then confirmed by a quantitative morphometry assessment on centrally digitized images using a dedicated morphometry software (Spine-X Analyzer ICAM Diagnostics, Milan, Italy) [12]. 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

Table 1 Clinical and demographical features of 32 males with prolactin (PRL)-secreting adenoma and 64 control subjects with normal PRL values

	PRL-secreting adenoma	Controls	*P*-values
Cases	32	64	
Age (years)	47 (22–79)	45 (26–79)	0.87
Parental history of fractures	12.5%	15.6%	0.68
Current cigarette smoking	34.4%	42.2%	0.46
High alcohol consumption	6.3%	4.7%	0.74
Serum PRL (ng/ml)	98 (3.3–1800)	7 (4–13)	<0.001
BMD ≤ -1 SD	59.4%	21.9%	<0.001
Size of adenomas (M/m)	22/10		
Duration of disease (years)	4 (1–10)		
Serum IGF-I values (ng/ml)	142 (19–300)		
Hypogonadism	78.1%	0	<0.001
Hypothyroidism	59.3%	0	<0.001
Glucocorticoid deficiency	65.6%	0	<0.001
Diabetes insipidus	6.2%	0	<0.001
Cabergoline therapy	71.9%	0	<0.001

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

20–25%, 25–40% and more than 40%, respectively [12]. The morphometric analysis was performed by a single operator (G.M.) who was blinded to the identity of patients.

Biochemical measurements

Blood samples were collected after an overnight fast. Serum was promptly separated and stored at –20°C until assay. Chemiluminescence immunoassay systems were used to measure serum PRL (Cobas, Roche) and insulin-like growth factor-1 (IGF-1) (Immulite, DPC). The normal PRL values were 4–15 ng/ml. For IGF-I, normal ranges were 136–244, 107–181 and 97–159 ng/ml for men aged 20–49, 40–59 and 60–79 years, respectively. Serum total testosterone was measured by a RIA. The normal range for men aged 20–49 years was 2.6–15.9 ng/ml, and for men >50 years it was 1.8–7.5 ng/ml.

Statistical analysis

All data were expressed as the median and range. Un-paired data were compared using Mann–Whitney test. Frequencies were compared using χ^2 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

Thirteen patients (40.6%) with PRL-secreting adenomas had normal BMD T-score, whereas osteopenia was observed in 15 patients (46.9%) and osteoporosis in 4 patients (12.5%). The prevalence of BMD T-score ≤ -1.0 SD was significantly ($P < 0.001$) higher in patients with prolactinoma as compared to control subjects (Table 1). Patients with prolactinoma showed higher prevalence of hypogonadism as compared to control subjects, whereas no significant differences in parental history of fractures, cigarette smoking and high-alcohol consumption were observed between the two groups (Table 1).

Vertebral fractures were shown in 12 patients with PRL-secreting adenoma (37.5%) and in 5 controls (7.8%, $P < 0.001$). In patients with prolactinoma, six had single fractures and 6 two or more fractures. Fractures were mild in six patients, moderate in four and severe in the other two fractured men with PRL-secreting adenoma. The frequencies of severe and multiple fractures were not significantly different between fractured patients and controls.

Multivariate logistic regression analysis in the whole population of patients and control subjects demonstrated that the correlation between PRL-secreting adenoma and vertebral fractures was independent of the effects of hypogonadism (odds ratio: 8.8, C.I. 95% 1.50–51.1; $P = 0.01$).

Fractured patients with prolactinoma had lower BMD T-score and longer duration of disease as compared to patients who did not fracture, without any significant difference in age, serum IGF-I and PRL values, frequency of macroadenomas, adrenal insufficiency, hypothyroidism, diabetes insipidus, parental history of fractures, cigarette smoking and high intake of alcohol (Table 2). Fractures occurred more frequently in patients with untreated hyperprolactinemia versus patients treated with cabergoline (66.7% vs. 26.1%; $P = 0.03$). However, in these latter patients the frequency of vertebral fractures was still significantly ($P = 0.02$) higher as compared to control subjects.

The prevalence of vertebral fractures was not significantly ($P = 0.8$) different between eugonadal and hypogonadal patients (Fig. 1). The prevalence of vertebral fractures was comparable in patients with untreated hypogonadism and in those with hypogonadism under long-term treatment with testosterone (37.5% vs. 33.3%; $P = 0.83$). Moreover, no significant difference in serum testosterone values was found between fractured and not fractured males (1.9 ng/ml, range: 0.3–8.1 vs. 1.6 ng/ml, range: 0.6–12.1; $P = 0.4$).

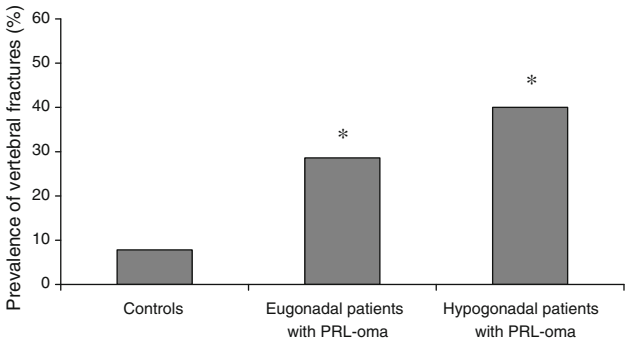

Fig. 1 Prevalence of vertebral fractures in eugonadal ($n = 7$) and hypogonadal ($n = 25$) males with prolactin-secreting adenoma (PRL-oma) as compared to control subjects ($n = 64$). *$P < 0.05$ patients versus controls

Discussion

This cross-sectional study shows that radiological vertebral fractures occurred in more than one-third of males with PRL-secreting pituitary adenomas. Vertebral fractures were significantly associated with duration of disease and BMD, independently of the effects of hypogonadism.

Bone loss occurs frequently in patients with hyperprolactinemia and the authors recently observed high prevalence of vertebral fractures in women with prolactinoma [8]. Vertebral fractures are clinically important since they impact the outcome of patients with osteoporosis in terms of development of new fractures and increase in morbility and mortality [13, 14]. In this study, it was observed high prevalence of vertebral fractures also in males with prolactinoma, providing evidence that osteoporotic fractures may be a general complication of hyperprolactinemia.

It is noteworthy that the high rate of vertebral fractures in hyperprolactinemia was not restricted to hypogonadal patients, but occurred also in patients with normal gonadal function. This finding is in line with the previous data from women with prolactinoma [8] and consistent with the hypothesis that hyperprolactinemia may have sex hormone-independent effects on bone remodelling [15–20]. The association between vertebral fractures and duration of hyperprolactinemia in the patients is also consistent with this intriguing hypothesis that, however, needs to be confirmed in further clinical studies with a larger population of eugonadal and hypogonadal patients.

In the general population, the risk of vertebral fractures is related to BMD [21]. Also in the males with prolactinoma, 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 patients, whereas only 12% of patients were osteoporotic at DXA. This finding is consistent with the hypothesis that in

Table 2 Historical, clinical and biochemical data in fractured and not fractured patients with prolactin (PRL)-secreting adenoma

	Patients with PRL-secreting adenoma		
	Fractured	Not fractured	*P*-values
Cases	12	20	
Age (years)	49 (22–73)	46 (24–79)	0.8880
Parental history of fractures	16.7%	10.0%	0.62
Current cigarette smoking	33.3%	30.0%	0.84
High alcohol consumption	8.3%	5.0%	0.71
Serum PRL (ng/ml)	198 (35–1800)	49 (3–807)	0.07
BMD T-score (SD)	−1.5 (from −2.8 to −0.8)	+0.05 (from −2.9 to +1.5)	0.007
Size of adenomas (M/m)	8/4	14/6	0.84
Duration of disease (years)	10.5 (4–20)	3.0 (1–7)	<0.001
Serum IGF-I values (ng/ml)	152 (19–300)	142 (35–250)	0.58
Hypogonadism	83.3%	75.0%	0.58
Hypothyroidism	50.0%	65.0%	0.40
Glucocorticoid deficiency	66.7%	65.0%	0.92
Diabetes insipidus	8.3%	5.0%	1
Cabergoline therapy	50.0%	85.0%	0.03

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

secondary osteoporosis fracture threshold is lower than in male idiopathic and post-menopausal osteoporosis [22–26] and that PRL excess may impair more significantly bone quality than bone quantity [27].

Dopaminergic drugs are the mainstay of treatment in patients with prolactinoma [28]. In a previous study, the prevalence of vertebral fractures was significantly higher in women with untreated hyperprolactinemia as compared to women whose disease was treated by cabergoline [8]. This trend was confirmed also in men with prolactinoma. However, differently from women, men with treated prolactinoma showed a prevalence of vertebral fractures which was still higher than the control subjects, suggesting that dopaminergic drugs may only partially revert the risk of fractures in these patients. This finding is in agreement with previous observations which demonstrated that dopaminergic drugs only led to a partial recovery of hyperprolactinemia-induced bone loss, as assessed by BMD measurement, especially when the disease was long-standing [29, 30].

This study has some limitations. The prevalence of hypopituitarism was not consistently assessed in the patients [31–33] and the authors cannot exclude that growth hormone deficiency may have influenced the prevalence of vertebral fractures in some males with PRL-secreting macroadenoma [34]. However, the lack of association between vertebral fractures and the size of pituitary adenomas, which is an important determinant of the occurrence of growth hormone deficiency, 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 [35, 36]. In women with prolactinoma, the duration of hyperprolactinemia was shown to be the most important factor associated with vertebral fractures [8]. In this study, the low number of enrolled males did not allow to perform a multivariate analysis restricted to prolactinoma patients to assess the independent effects of duration of hyperprolactinemia, BMD and serum prolactin values on vertebral fractures. Furthermore, the small number of eugonadal and hypogonadal patients did not permit to investigate reliably the skeletal effects of gonadal status and the relative impact of BMD on fractures in these subgroups of patients with hyperprolactinemia. Future studies are needed to clarify these issues.

In conclusion, our data showed that hyperprolactinemia was associated with high prevalence of radiological vertebral fractures in males with PRL-secreting adenoma. The findings also suggested that fractures may occur even in osteopenic subjects and that a spine X-ray with morphometric analysis should be performed for a complete skeletal assessment in eugonadal and hypogonadal males with PRL-secreting adenoma.

Conflicts of interest None.

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

References

1. F.F. Casanueva, M.E. Molitch, J.A. Schlechte, R. Abs, V. Bonert, M.D. Bronstein, T. Brue, P. Cappabianca, A. Colao, R. Fahlbusch, H. Fideleff, M. Hadani, P. Kelly, D. Kleinberg, E. Laws, J. Marek, M. Scanlon, L.G. Sobrinho, J.A. Wass, A. Giustina, Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin. Endocrinol. **65**, 265–273 (2006)
2. A. Fernandez, N. Karavitaki, J.A. Wass, Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin. Endocrinol. **72**, 377–382 (2010)
3. T. Mancini, F.F. Casanueva, A. Giustina, Hyperprolactinemia and prolactinomas. Endocrinol. Metab. Clin. North Am. **37**, 67–99 (2008)
4. S.L. Greenspan, R.M. Neer, E.C. Ridgway, A. Klibanski, Osteoporosis in men with hyperprolactinemic hypogonadism. Ann. Intern. Med. **104**, 777–782 (1986)
5. S.L. Greenspan, D.S. Oppenheim, A. Klibanski, Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. Ann. Intern. Med. **110**, 526–531 (1989)
6. A. Shibli-Rahhal, J. Schlechte, The effects of hyperprolactinemia on bone and fat. Pituitary **12**, 96–104 (2009)
7. P. Vestergaard, J.O. Jørgensen, C. Hagen, H.C. Hoeck, P. Laurberg, L. Rejnmark, K. Brixen, J. Weeke, M. Andersen, F.L. Conceicao, T.L. Nielsen, L. Mosekilde, Fracture risk is increased in patients with GH deficiency or untreated prolactinomas—a case-control study. Clin. Endocrinol. **56**, 159–167 (2002)
8. G. Mazziotti, T. Mancini, M. Mormando, E. De Menis, A. Bianchi, M. Doga, T. Porcelli, P.P. Vescovi, L. De Marinis, A. Giustina, High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas. Pituitary. (2011). [Epub ahead of print] PubMed PMID: 21301967
9. G. Mazziotti, E. Canalis, A. Giustina, Drug-induced osteoporosis: mechanisms and clinical implications. Am. J. Med. **123**, 877–884 (2010)
10. J.A. Kanis, E.V. McCloskey, H. Johansson, O. Strom, F. Borgstrom, A. Oden, National osteoporosis guideline group: case finding for the management of osteoporosis with FRAX–assessment and intervention thresholds for the UK. Osteoporos. Int. **19**, 1395–1408 (2008)
11. J.A. Kanis, N. Burlet, C. Cooper, P.D. Delmas, J.Y. Reginster, F. Borgstrom, R. Rizzoli, European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO): European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos. Int. **19**, 399–428 (2008)
12. H.K. Genant, M. Jergas, L. Palermo, M. Nevitt, R.S. Valentin, D. Black, S.R. Cummings, 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 (1996)
13. M.C. Nevitt, B. Black, D.M. Black, K. Stone, S.A. Jamal, K. Ensrud, M. Segal, H.K. Genant, S.R. Cummings, The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann. Intern. Med. **128**, 793–800 (1998)
14. T. Jalava, S. Sarna, L. Pylkkänen, B. Mawer, J.A. Kanis, P. Selby, M. Davies, J. Adams, R.M. Francis, J. Robinson, E. McCloskey, Association between vertebral fracture and increased mortality in osteoporotic patients. J. Bone Miner. Res. **18**, 1254–1260 (2003)
15. J.A. Schlechte, B. Sherman, R. Martin, Bone density in amenorrheic women with and without hyperprolactinemia. J. Clin. Endocrinol. Metab. **56**, 1120–1123 (1983)
16. D. Coss, L. Yang, C.B. Kuo, X. Xu, R.A. Luben, A.M. Walker, Effects of prolactin on osteoblast alkaline phosphatase and bone formation in the developing rat. Am. J. Physiol. Endocrinol. Metab. **279**, E1216–E1225 (2000)
17. S. Lotinun, L. Limlomwongse, V. Sirikulchayanonta, N. Krishnamra, Bone calcium turnover, formation, and resorption in bromocriptine- and prolactin-treated lactating rats. Endocrine **20**, 163–170 (2003)
18. D. Seriwatanachai, N. Krishnamra, J.P. van Leeuwen, Evidence for direct effects of prolactin on human osteoblasts: inhibition of cell growth and mineralization. J. Cell. Biochem. **107**, 677–685 (2009)
19. D. Seriwatanachai, N. Charoenphandhu, T. Suthiphongchai, N. Krishnamra, 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 (2008)
20. D. Seriwatanachai, K. Thongchote, N. Charoenphandhu, J. Pandaranandaka, K. Tudpor, J. Teerapornpuntakit, T. Suthiphongchai, N. Krishnamra, Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio. Bone. **42**, 535–546 (2008)
21. S.C. Schuit, M. van der Klift, A.E. Weel, C.E. de Laet, H. Burger, E. Seeman, A. Hofman, A.G. Uitterlinden, J.P. van Leeuwen, H.A. Pols, Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone **34**, 195–202 (2004)
22. G. Mazziotti, A. Angeli, J.P. Bilezikian, E. Canalis, A. Giustina, Glucocorticoid-induced osteoporosis: an update. Trends Endocrinol. Metab. **17**, 144–149 (2006)
23. P. Vestergaard, 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 (2007)
24. T. Mancini, G. Mazziotti, M. Doga, R. Carpinteri, N. Simetovic, P.P. Vescovi, A. Giustina, Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone. **45**, 784–788 (2009)
25. G. Mazziotti, A. Bianchi, S. Bonadonna, V. Cimino, I. Patelli, A. Fusco, A. Pontecorvi, L. De Marinis, A. Giustina, Prevalence of vertebral fractures in men with acromegaly. J. Clin. Endocrinol. Metab. **93**, 4649–4655 (2008)
26. G. Mazziotti, T. Porcelli, I. Patelli, P.P. Vescovi, A. Giustina, Serum TSH values and risk of vertebral fractures in euthyroid post-menopausal women with low bone mineral density. Bone **46**, 747–751 (2010)
27. E. Canalis, A. Giustina, J.P. Bilezikian, Mechanisms of anabolic therapies for osteoporosis. N. Engl. J. Med. **357**, 905–916 (2007)
28. G. Iván, N. Szigeti-Csúcs, M. Oláh, G.M. Nagy, M.I. Góth, Treatment of pituitary tumors: dopamine agonists. Endocrine. **28**, 101–110 (2005)
29. C. Di Somma, A. Colao, A. Di Sarno, M. Klain, M.L. Landi, G. Facciolli, R. Pivonello, N. Panza, M. Salvatore, G. Lombardi, Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J. Clin. Endocrinol. Metab. **83**, 807–813 (1998)
30. A. Colao, C. Di Somma, S. Loche, A. Di Sarno, M. Klain, R. Pivonello, M. Pietrosante, M. Salvatore, G. Lombardi, Prolactinomas in adolescents: persistent bone loss after 2 years of prolactin normalization. Clin. Endocrinol. **52**, 319–327 (2000)
31. A. Giustina, R. Lorusso, V. Borghetti, G. Bugari, V. Misitano, O. Alfieri, Impaired spontaneous growth hormone secretion in severe dialated cardiomyopathy. Am. Heart J. **131**, 620–622 (1996)
32. E. Ghigo, G. Aimaretti, E. Arvat, F. Camanni, Growth hormone-releasing hormone combined with arginine or growth hormone secretagogues for the diagnosis of growth hormone deficiency in adults. Endocrine. **15**, 29–38 (2001)
33. M. Doga, S. Bonadonna, M. Gola, S.B. Solerte, G. Amato, C. Carella, A. Giustina, Current guidelines for adult GH replacement. Rev. Endocr. Metab. Disord. **6**, 63–70 (2005)
34. A. Giustina, G. Mazziotti, E. Canalis, Growth hormone, insulin-like growth factors, and the skeleton. Endocr. Rev. **29**, 535–559 (2008)
35. G. Mazziotti, A. Bianchi, S. Bonadonna, M. Nuzzo, V. Cimino, A. Fusco, L. De Marinis, A. Giustina, Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. J. Bone Miner. Res. **21**, 520–528 (2006)
36. G. Mazziotti, A. Bianchi, V. Cimino, S. Bonadonna, P. Martini, A. Fusco, L. De Marinis, A. Giustina, Effect of gonadal status on bone mineral density and radiological spinal deformities in adult patients with growth hormone deficiency. Pituitary. **11**, 55–61 (2008)