Prevalence of osteopenia in men with prolactinoma

E.C.O. Naliato, M.L.F. Farias, G.R. Braucks, F.S.R. Costa, D. Zylberberg, and A.H.D. Violante

Division of Endocrinology, Department of Internal Medicine, Federal University of Rio de Janeiro (UFRJ) and University Hospital Clementino Fraga Filho (HUCFF), Brazil

ABSTRACT. The aim of this cross-sectional study was to analyze bone mineral density (BMD) and prevalence of osteopenia and osteoporosis in 30 men with prolactinoma, and compare them to 22 control subjects. BMD of lumbar spine and femur was evaluated by dual-energy X-ray absorptiometry. PRL, testosterone, estradiol, sexual hormone-binding globulin and free androgen and estrogen indexes (FAI and FEI, respectively) were measured in all the subjects. In patients with prolactinoma, mean values of PRL and testosterone were calculated for the 12-month period that preceded the study. The mean T-score of the four sites analyzed by bone densitometry was lower in men with prolactinoma than in controls (*p*-values: lumbar spine=0.015, femoral neck <0.0001, trochanter=0.037, total femur=0.036), and 55.6% of the former presented osteopenia or osteoporosis at one or more sites (*p*=0.035). The lumbar spine was the most seriously affected site, where 29.6% had osteopenia and 14.8% had osteoporosis. By the time of BMD determination, significant associations were found between BMD and PRL, testosterone, FAI, estradiol, FEI, and duration of hypogonadism. Considering the period of 12 months that preceded BMD evaluation, trochanter BMD was associated with mean PRL levels, while there was an association between lumbar spine BMD and mean testosterone levels. However, the multiple regression analysis showed that estradiol was the main determinant of BMD. In conclusion, men with prolactinoma have high prevalence of osteopenia and osteoporosis. Bone loss in such patients is associated with hyperprolactinemia and hypogonadism, and mainly influenced by estrogen.

(J. Endocrinol. Invest. 28: 12-17, 2005)

INTRODUCTION

Hyperprolactinemia is considered a risk factor for the development of osteopenia (1), either due to secondary hypogonadism or to the maintenance of high levels of PRL *per se*. Bone loss is usually progressive (2, 3), but the adequate control of hyperprolactinemia and hypogonadism can interrupt this process and lead to partial recovery of bone mineral density (BMD) (2, 4-6). Bone density impairment is more severe in children and adolescents than in adults with hyperprolactinemia (6, 7).

Most studies on the relationship between hyperprolactinemia and BMD have focused on women. Although the prevalence of hyperprolactinemia and osteopenia is lower in men than in women, studies have shown that hyperprolactinemic men are also prone to develop osteopenia (4-6, 8).

The aim of the present study was to determine the prevalence of osteopenia and osteoporosis in men with prolactinoma, and analyze the relationship between bone density, hyperprolactinemia and hypogonadism.

MATERIALS AND METHODS

Thirty men with prolactinoma, aged 17 to 67 yr (mean±SD: 42±14 yr), were included in this cross-sectional study. Three of them had developed hyperprolactinemia during adolescence and 27 in adulthood. By the time of bone density evaluation, all the adolescents had already completed pubertal development. Twenty-two healthy subjects, matched for gender, age, and BMI, served as control group (Table 1). The two groups were also similar in terms of risk factors for osteopenia, such as family history, previous trauma-related fractures, alcohol ingestion, smoking and physical inactivity. There were no cases of fragility fractures either in the patient or control group.

The diagnosis of prolactinoma had been established on the basis of clinical features, PRL levels (>100 ng/ml for microprolac-

Key-words: Bone density, prolactinoma, hypogonadism, men, densitometry.

Correspondence: E.C.O. Naliato, MD, Av Lucio Meira 670 sala 517, Centro, Teresópolis/RJ 25953-003, Brazil.

E-mail: erikanaliato@uol.com.br

Accepted August 3, 2004.

Table 1 - *Clinical, hormonal and bone densitometry data of patients and controls.*

	Patients	Controls	*p*
No. of subjects	30	22	-
Age (yr)	42±14	41±13	0.967
BMI (kg/m²)	28.4±4.3	27.7±4.7	0.967
Disease duration (months)	48±42	-	-
Duration of hypogonadism	40±44	-	-
Lumbar spine BMD (g/cm²)	1.118±0.204	1.210±0.149	0.043
Lumbar spine T-score (SD)	–0.7±1.5	0.0±1.0	0.015
Lumbar spine Z-score (SD)	–1.2±1.7	–0.1 ±1.0	0.013
Femoral neck BMD (g/cm²)	1.055±0.215	1.061±0.121	0.673
Femoral neck T-score (SD)	–0,1±1.7	0.0±0.9	0.006
Femoral neck Z-score (SD)	0.1±1.3	0.2 ±0.8	0.045
Trochanter BMD (g/cm²)	0.908±0.197	0.929±0.125	0.480
Trochanter T-score (SD)	–0.1±1.9	0.0±1.1	0.037
Trochanter Z-score (SD)	–0.1±1.6	0.1±1.0	0.040
Total femur BMD (g/cm²)	1.117±0.203	1.109±0.125	0.950
Total femur T-score (SD)	0.2±1.6	0.2±0.9	0.037
Total femur Z-score (SD)	0.3±1.3	0.3±0.9	0.199
PRL (ng/ml or µg/l)	781.2±2804.5	7.6±2.7	<0.0001
Testosterone (ng/dl)	304.4±198.4	489.6±201.3	0.0008
Estradiol (pg/ml)	34.3±12.2	38.8±9.2	0.258
SHBG (nmol/l)	29.0±23.5	27.4±9.4	0.354
FAI	495.5±448.7	699.2±359.8	0.087
FEI	6.8±6.5	6.4±2.5	0.883
FSH (IU/ml)	3.6±3.2	4.3±3.1	0.092
LH (IU/ml)	2.7±2.3	3.9±2.2	0.004
PRL previous 12 months (ng/ml)	1508.2±4133.8	-	-
Testosterone previous 12 months (ng/dl)	294.5±186.7	-	-
PTH (pg/ml)	24.8±12.5	39.3±19.5	0.005
Calcium (mg/dl)	8.8±0.5	9.0±0.4	0.185
Phosphorus (mg/dl)	3.7±0.7	3.5±0.8	0.468
Creatinine (mg/dl)	0.9±0.1	0.9±0.2	0.642
Alkaline phosphatase (IU/l)	105.0±60.6	102.2±87.3	0.606

BMI: body mass index; BMD: bone mineral density; FAI: free androgen index; FEI: free estrogen index; CF: conversion factor; ISU: international system units. Normal range: PRL = 2.5-17 ng/ml (or µg/l); testosterone = 270-1734 ng/dl (20-40 yr) and 212-755 ng/dl (>50 yr; CF for ISU = 0.04467); Estradiol = undetectable – 56 pg/ml (CF for ISU = 3.671); SHBG = 13 – 71 nmol/l; FSH = 0.7-11.1 IU/l; LH = 0.8-7.6 IU/l; PTH = 7-56 pg/ml (CF for ISU = 3.671). Data expressed in mean±SD. Statistical significance when $p \leq 0.05$.

tinomas and >200 ng/ml for macroprolactinomas) and the presence of a pituitary adenoma at computed tomography and/or magnetic resonance imaging. The mean time elapsed since the diagnosis was 48 months. Twenty-seven patients had macroadenomas and 3 microadenomas; twelve of them had been previously submitted to surgery (mean±SD time elapsed since the procedure=49±40 months) and 2 to radiotherapy (one of them 24 months and the other 108 months before the present study), but had not achieved adequate control of hyperprolactinemia with non-pharmacological therapies. All patients were in treatment with dopamine agonists by the time of bone density evaluation (18 with bromocriptine and 12 with cabergoline). It had been initiated 28±21 months before (bromocriptine: 28±21 months and cabergoline: 15±15 months; $p=0.075$). The pituitary function of these patients had been evaluated by the time of their referral to the endocrine clinic of the University Hospital Clementino Fraga Filho and also whenever necessary during the follow-up and by the time of BMD evaluation. Eight patients had GH deficiency, but none had received GH replacement before this study. GH deficiency had been diagnosed 45±39 months before BMD evaluation (peak GH levels during the insulin tolerance test in the GH-deficient=2.1±1.6 ng/ml *vs* 15.4±1.6 ng/ml, in those without GH-deficiency; $p<0.0001$). Nine patients had secondary hypothyroidism, 7 had secondary adrenal insufficiency, and 1 had diabetes insipidus; all of them were well controlled with levothyroxine, glucocorticoid and DDAVP administration, respectively. By the time of BMD determination, 20% complained of erectile dysfunction or decreased libido, and the mean duration of hypogonadism corresponded to 40±44 months.

Lumbar spine (L2-L4) and hip (femoral neck, trochanter and total femur) BMD were evaluated by dual energy x-ray absorptiometry in a DPX-L analyzer (Lunar Corp.). In addition, the study protocol included the measurement of serum PRL, testosterone, estradiol, SHBG, free androgen and estrogen indexes (FAI and FEI, respectively), FSH, LH, PTH, TSH, free T_4, cortisol, GH, and IGF-I by specific immunoassays using commercially available kits. Mean values of PRL and testosterone were calculated for the period of 12 months previous to the present study. Calcium, phosphorus, creatinine, and alkaline phosphatase were assayed using standard methods, in our laboratory.

Bone density data were expressed as BMD (g/cm²), T-score (comparison to the young adult) and Z-score (comparison to age-matched men). Subjects were considered osteopenic when they had a T-score between –1 and –2.5 SD and osteoporotic when T-score was <–2.5 SD, while T-scores >–1 SD were compatible with normal bone mass. Subjects younger than 12 yr old were compared only to the age-matched population (Z-score).

In the statistical analysis, unpaired t-test was used to compare means (except in the absence of normal distribution, when the Mann-Whitney test was used) and Fisher's exact test to compare categorical variables. Relationships between two numeric variables were studied by linear regression and Pearson's linear correlation, while multiple regression was employed for the multivariate analysis. The significance was set as 5%.

RESULTS

Bone densitometry results

The mean T-score of the four sites analyzed by bone densitometry was lower in men with prolactinoma than in controls (*p* values: lumbar spine=0.015, femoral neck <0.0001, trochanter=0.037, total femur=0.036; Table 1). More than half of the patients (55.6%) had T-scores lower than –1 SD (osteopenia or osteoporosis) at one or more skeletal sites, which resulted in a higher prevalence of low bone density, when compared to controls ($p=0.035$). Lumbar spine was the most seriously affected site, characterized by 29.6% of osteopenic patients and 14.8% of osteoporotic ones, followed by the femoral neck, where 22.2% had osteopenia and 11.1% osteoporosis. At the trochanter, the prevalence of osteopenia equaled that of the femoral neck (22.2%) and 7.7% had osteoporosis. There were no cases of osteoporosis at the total femur, but 18.5% were osteopenic (Fig. 1).

Lumbar spine BMD was significantly lower in patients with prolactinoma than in controls (1.118±0.204 *vs* 1.210±0.150 g/cm²; $p=0.048$; Table 1). Despite ns differences between groups regarding femoral neck, trochanter and total femur BMD, the values of bone density at these three sites were extremely correlated to lumbar spine BMD ($p<0.0001$ for each association).

The mean Z-score of the three sites was also lower in patients than in controls (*p* values: lumbar spine=0.013, femoral neck=0.045, trochanter=0.04);

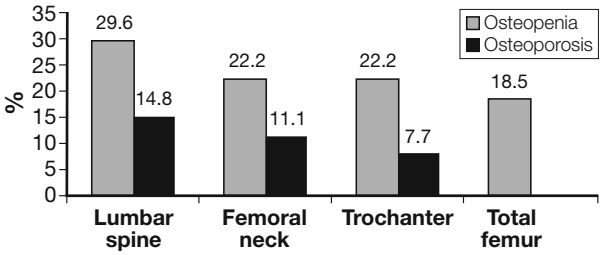

Fig. 1 - *Prevalence of osteopenia and osteoporosis in 30 men with prolactinoma.*

(Table 1). Thirty % of patients (*vs* zero controls) had a Z-score lower than –2 SD in one or more skeletal sites ($p=0.004$). Lumbar spine was the site with the highest percentage of cases of Z-score lower than –2 SD (26.7%), followed by trochanter (13.3%) and femoral neck (10%), with no cases at the total femur.

There was an association between age and BMD at lumbar spine (r=–0.403; $p=0.003$), femoral neck (r=–0.441; $p=0.002$) and total femur (r=–0.305; $p=0.05$). Although the small number of adolescents included in the study did not allow the performance of statistical analysis separately, we observed that the three adolescents with prolactinoma had the lowest Z-scores of this study.

Subjects with positive family history of osteopenia ($p=0.01$) and regular consumption of alcoholic beverages ($p=0.01$) had lower lumbar spine BMD. Patients who presented additional GH deficiency had lower Z-scores at lumbar spine (–2.0±1.4 *vs* –0.5±1.7 SD; $p=0.013$) and femoral neck (–0.7±0.9 *vs* 0.3±1.1 SD; $p=0.036$) than those non-GH deficient.

Control of hyperprolactinemia and hypogonadism vs *BMD*

Hormonal and biochemical evaluation excluded the presence of other secondary causes of osteopenia. By the time of bone density determination, levels of PRL (mean±SD: 781.2±2804.5 *vs* 7.6±2.7 ng/ml, median: 28.5 *vs* 7.3 ng/ml; $p<0.0001$) and testosterone (mean±SD: 304.4±198.4 *vs* 489.6±201.3 ng/dl, median: 290.5 *vs* 441.8; $p=0.0008$) differed significantly when patients and controls were compared (Table 1). Eighty % of patients had PRL levels above the normal range for men (2.5-17.0 ng/ml). There was a negative association between PRL levels and lumbar spine BMD (r=–0.34; $p=0.013$).

Testosterone levels were negatively associated with those of PRL (r=–0.606; $p<0.0001$). Forty-three % of the patients had testosterone levels below the normal range for men (age 20 to 49 yr: 270-1734 ng/dl, and ≥50 yr: 212-755 ng/dl). Lumbar spine BMD was positively associated with

testosterone levels (r=0.334; p=0.015) and FAI (r=0.348; p=0.012).
Thirteen patients (43.3%) and 8 controls (36.4%) had undetectable estradiol levels. At the four sites analyzed by bone densitometry, the absence of detectable levels of estradiol was associated with lower BMD (p=0.04 at lumbar spine, 0.049 at femoral neck, 0.005 at trochanter and 0.022 at total femur). BMD was positively associated with estradiol levels at lumbar spine (r=0.423; p=0.028) and trochanter (r=0.498; p=0.013). Lumbar spine BMD was also associated with free estrogen levels (r=0.466; p=0.014).

Control of hyperprolactinemia and hypogonadism (during the previous 12 months) vs *BMD*

During the 12-month period that preceded bone density evaluation, mean serum PRL levels in the patients' group corresponded to 1508.2±4133.8 ng/ml (Table 1). The mean PRL levels of 73.3% of patients were above the normal range. We identified an association between mean 12-month PRL levels and trochanter BMD (r=–0.393; p=0.047). However, there was no correlation between time elapsed since the diagnosis of prolactinoma, age at diagnosis or initial PRL levels and BMD at any site.
Most patients (83.3%) had clinical features of hypogonadism during the evolution of the prolactinoma, but only 10% had been treated for more than 6 months with testosterone replacement. For the period of 12 months that preceded bone density evaluation, mean serum testosterone levels were 294.5±186.7 ng/dl (Table 1) and 43.3% of patients presented levels below the normal range. Similarly to what was observed for the serum analysis performed by the time of BMD determination, testosterone levels were negatively associated with those of PRL (r=–0.538; p=0.002). A positive association between mean 12-month testosterone levels and BMD at lumbar spine (r=0.367; p=0.045) and femoral neck (r=0.379; p=0.05) was found. There was also a trend towards significance for the association between 12-month testosterone levels and trochanter (r=0.335; p=0.094) and total femur BMD (r=0.341; p=0.087). The duration of hypogonadism was greater in patients who had osteopenia or osteoporosis in one or more sites (43 *vs* 10 months, p=0.006). Lumbar spine BMD was correlated with the duration of hypogonadism (r=0.473; p=0.012).

Multiple regression results

Multiple regression models were created to identify factors that had significantly affected spine and femoral BMD. After the adjustment for the influence of other variables, we observed that estradiol levels made the decisive contribution for lumbar spine (coefficient=0.176, p=0.009) and trochanter BMD (coefficient=0.328, p=0.03). On the other hand, age was the main determinant of femoral neck (coefficient=5.858, p=0.042) and total femur BMD (coefficient=3.111, p=0.049) (Table 2).

DISCUSSION

In spite of the fact that the general prevalence of fractures is lower in men than in women, fracture risk is higher in men than in women with the same BMD (9).
Our results show that men with hyperprolactinemia and hypogonadism have higher prevalence of osteopenia in one or more skeletal sites and consequently increased fracture risk (10). Their BMD is also significantly lower, which detached from values of T-score has more statistical than clinical impact. Besides the findings that resulted from the comparison with the young adults, significantly lower Z-scores showed that the patients' BMD was also inferior to that of age-matched men. These data are in agreement with other studies developed with hyperprolactinemic men (4, 6, 8).
In accordance to previous data in both women and men (4, 6, 12), the skeletal site with the highest prevalence of osteopenia in the present study was the lumbar spine. It is formed mostly by trabecular bone (11), which is particularly susceptible to endocrine disturbances, such as hyperprolactinemia and hypogonadism (4, 6, 12-13). It was suggested that trabecular bone is damaged earlier than cortical bone in patients with hyperprolactinemia (6). In fact, our data show a relationship between prevalence of osteopenia at either trabecular (lumbar spine) or cortical bone (femoral neck) and the duration of hypogonadism.
Our results on adolescents with prolactinoma were similar to those from Di Somma et al. (6) and Colao et al. (7), who found that patients who develop hyperprolactinemia in childhood or adolescence have more severe bone impairment than the ones in which hyperprolactinemia starts in adulthood. Adequate control of hyperprolactinemia seems insufficient to restore bone mass in younger patients (7).
Although not reported by other studies of BMD in hyperprolactinemia, family history and alcohol consumption are known risk factors for the development of osteopenia (9, 14), and our data confirm the

Table 2 - *Multiple regression results.*

Site	Factor	coefficient	p
Lumbar spine	Estradiol	0.176	0.009
Femoral neck	Age	5.858	0.042
Trochanter	Estradiol	0.328	0.030
Total femur	Age	3.111	0.049

Statistical significance when $p \leq 0.05$.

existence of an association between these factors and bone loss in hyperprolactinemic men. Another feature that was analyzed in the present study, GH deficiency constitutes an important risk factor for osteopenia and fractures (15). Among the pituitary hormones, GH deficiency is the one that most severely impairs BMD (16). Even in non-deficient subjects aged 20 to 40 yr, there is an association between bone mass and GH levels (17). When GH deficiency occurs during childhood or puberty, it limits bone acquisition and, as a consequence, younger individuals tend to present greater BMD impairment (18). In our patients with prolactinoma and GH deficiency, BMD was significantly lower than in the patients with prolactinoma without GH deficiency. Thus, even in our small selected group, GH deficiency was confirmed to have a negative effect on bone mass.

Bone loss is usually progressive in patients with hyperprolactinemia and hypogonadism (2, 3), but non-amenorrheic hyperprolactinemic women do not present a decrease in BMD, which reinforces the role of hypogonadism on bone loss in hyperprolactinemia (3, 19-21). Hypogonadism has been linked with decreased bone density in men with constitutional delayed puberty (22), hypogonadrotropic hypogonadism (23) and in treatment with agonists of GnRH (24). Most men with hyperprolactinemia develop secondary hypogonadism (25, 26), which seems to be the major cause of bone loss in these patients rather than a direct effect of hyperprolactinemia on bone metabolism (3-5, 8, 18, 27). Similarly to our data, duration of hypogonadism has been associated with the extent of bone loss in studies with men and women with hyperprolactinemia (3-5, 27-28). Nevertheless, some authors have identified a relationship between the degree of bone damage and duration of hyperprolactinemia and/or serum PRL levels (4, 6-7). Furthermore, adequate control of hyperprolactinemia and particularly of the associated hypogonadism can interrupt the bone loss and lead to partial recovery of BMD (2, 4-6).

In our study, by the time of bone density determination, the control of hyperprolactinemia and hypogonadism reflected the one observed during the previous 12 months: most patients had PRL levels above the normal range and more than a third had testosterone levels below the normal range. The association between testosterone levels and BMD confirms data from other studies on men (4, 5, 8), while the association between PRL and BMD was also observed by Di Somma et al. (6).

Considering that men with hypogonadism do not suffer solely from isolated deficiency of testosterone, but also lose substratum for the synthesis of estradiol, it is difficult to determine which deficit is the main cause of bone loss. To the best of our knowledge, previous studies on men with prolactinomas did not analyze the influence of estradiol levels on BMD. On the other hand, it is known that men with abnormalities of the estrogen receptor or aromatase deficiency, and consequent inability to respond to or produce estrogen, respectively, present failure of bone mineralization and maturation (29, 30). The linkage between estrogen levels and BMD seems to be independent of testosterone influence (31) and is also observed in the elderly (32). In our group of men with prolactinomas, the absence of detectable levels of estradiol was correlated with lower BMD in all sites. Klibanski et al. (28) and Carlsen et al. (33) found the same influence in women with hyperprolactinemia and men with osteoporosis, respectively. Our results from the multiple regression analysis show that the influence of estradiol on bone mass of men with prolactinoma was superior than the one exerted by testosterone and reinforce the critical role of estradiol on the pathogenesis of osteopenia in men.

Bioavailable fractions of testosterone and estradiol tend to drop with age due to the increase in SHBG levels. Men with lower bioavailable estradiol levels have enhanced bone turnover and lower BMD, which suggests that estradiol may be responsible for bone loss in the elderly (34). In the present study, FAI and FEI were associated with lumbar spine BMD. However, half of patients had undetectable estradiol level, which restricted the analysis of FEI and the establishment of correlations with BMD at the femoral sites.

In conclusion, the present study shows a high prevalence of osteopenia and osteoporosis in men with prolactinoma. The degree of bone loss is negatively associated with biochemical control of hyperprolactinemia and hypogonadism, being noticeably influenced by the estradiol levels. Trabecular bone is mainly affected, but cortical bone loss is also observed, which suggests that both lumbar spine and proximal femur BMD must be analyzed in order to properly evaluate the extension of bone loss in each case. Diagnosis and treatment of osteopenia constitute additional important issues to be considered in management of men with prolactinoma.

ACKNOWLEDGMENTS

We are grateful to Dr A. L. Tabet and Dr M. R. Gadelha for referring patients to this study.

REFERENCES

1. Vartej P, Poiana C, Vartej I. Effects of hyperprolactinemia on osteoporotic fracture risk in premenopausal women. Gynecol Endocrinol 2001,15: 43-7.

2. Klibanski A, Greenspan S. Increase in bone mass after treatment of hyperprolactinemic amenorrhea. N Engl J Med 1986, 315: 542-6.
3. Biller B, Baum H, Rosenthal D, Saxe V, Charpie P, Klibanski A. Progressive trabecular osteopenia in women with hyperprolactinemic amenorrhea. J Clin Endocrinol Metab 1992, 75: 692-7.
4. Greenspan S, Neer R, Ridgway E, Klibanski A. Osteoporosis in men with hyperprolactinemic hypogonadism. Ann Intern Med 1986, 104: 777-82.
5. Greenspan SL, Oppenheim D S, Klibanski A. Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. Ann Intern Med 1989, 110: 526-31.
6. Di Somma C, Colao A, Di Sarno A, et al. Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J Clin Endocrinol Metab 1998, 83: 807-13.
7. Colao A, Di Somma C, Loche S, et al. Prolactinomas in adolescents: Persistance of bone loss after 2 years of prolactin normalization. Clin Endocrinol (Oxf) 2000, 52: 319-27.
8. Jackson J, Kleerekoper M, Parfitt M. Symptomatic osteoporosis in a man with hyperprolactinemic hypogonadism. Ann Intern Med 1986, 105: 543-5.
9. Prelevic G. Osteoporosis in men. J R Soc Med 2001, 94: 620-3.
10. Cummings S, Black D, Nevitt M, et al. Bone density at various sites for prediction of hip fractures. Lancet 1993, 341: 72-5.
11. Bonnick SL. Densitometric anatomy. In: Bonnick SL eds. Bone densitometry in clinical practice. Totowa, New Jersey: Humana Press Inc. 1998, 31-64.
12. Schlechte J, El-Khoury G, Kathol M, Walkner L. Forearm and vertebral bone mineral in treated and untreated hyperprolactinemic amenorrhea. J Clin Endocrinol Metab 1987, 64: 1021-6.
13. Benito M, Gomberg B, Wehrli F, et al. Deterioration of trabecular architecture in hypogonadal men. J Clin Endocrinol Metab 2003, 88: 1497-502.
14. Seeman E, Melton III L, O'Fallon W, Riggs B. Risk factors for spinal osteoporosis in men. Am J Med 1983, 75: 977-83.
15. Vestergaard P, Jorgensen J, Hagen C, et al. Fractures risk is increased in patients with deficiency or untreated prolactinomas – a case-control study. Clin Endocrinol (Oxf) 2002, 56: 159-67.
16. Colao A, Di Somma C, Piovonello R, et al. Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. J Clin Endocrinol Metab 1999, 84: 1919-24.
17. Byers R, Hoyland J, Braidman I. Osteoporosis in men: a cellular endocrine perspective of an increasingly common clinical problem. J Endocrinol 2001, 168: 353-62.
18. Holmes S, Economou G, Whitehouse R, Adams J, Shalet S. Reduced bone mineral density in patients with adult onset growth hormone deficiency. J Clin Endocrinol Metab 1994, 78: 669-74.
19. Ciccarelli E, Savino L, Carlevatto V, Bertagna A, Isaia G, Camanni F. Vertebral bone density in non-amenorrheic hyperprolactinaemic women. Clin Endocrinol (Oxf) 1988, 28: 1-6.
20. Klibanski A, Biller B, Rosenthal D, Schoenfeld D, Saxe V. Effects of prolactin and estrogen deficiency in amenorrheic bone loss. J Clin Endocrinol Metab 1988, 67: 124-30.
21. Nystrom E, Leman J, Lundberg P, et al. Bone mineral content in normally menstruating women with hyperprolactinaemia. Horm Res 1988, 29: 214-7.
22. Finkelstein J, Klibanski A, Neer R. A longitudinal evaluation of bone mineral density in adult men histories of delayed puberty. J Clin Endocrinol Metab 1996, 81: 1152-5.
23. Guo C, Jones T, Eastell R. Treatment of isolated hypogonadotropic hypogonadism effect on bone mineral density & bone turnover. J Clin Endocrinol Metab 1997, 82: 658-65.
24. Mittan D, Lee S, Miller E, Perez R, Basler J, Bruder J. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 2002, 87: 3656-61.
25. Carter J, Tyson J, Tolis G, Van Vliet S, Faiman C, Friesen H. Prolactin-secreting tumors and hypogonadism in 22 men. N Engl J Med 1978, 299: 847-52.
26. Pinzone J, Katznelson L, Danila D, Pauler D, Miller C, Klibanski A. Primary medical therapy of micro- and macroprolactinomas in men. J Clin Endocrinol Metab 2000, 85: 3053-7.
27. Kayath M, Lengyel A, Vieira J. Prevalence and magnitude of osteopenia in patients with prolactinoma. Braz J Med Biol Res 1993, 26: 933-41.
28. Klibanski A, Neer R, Beitins I, Ridgway C, Zervas N, McArthur J. Decreased bone density in hyperprolactinemic women. N Engl J Med 1980, 303: 1511-4.
29. Braidman I, Baris C, Wood L, et al. Preliminary evidence for impaired estrogen receptor-alpha protein expression in osteoblasts and osteocytes from men with idiopathic osteoporosis. Bone 2000, 26: 423-7.
30. Morishima A, Grumbach M, Simpson E, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995, 80: 3689-98.
31. Ohgphipadhanakul B, Rajatanavin R, Chanprasertyothin S, Oiaseu N, Chailurkit L. Serum oestradiol and oestrogen-receptor gene polymorphism are associated with bone mineral density independently of serum testosterone in normal males. Clin Endocrinol (Oxf) 1998, 49: 803-9.
32. Center JR, Nguyen TV, Sambrook PN, Eisman JA. Hormonal and biochemical parameters in the determination of osteoporosis in elderly men. J Clin Endocrinol Metab 1999, 84: 3626-35.
33. Carlsen CG, Soerensen TH, Eriksen EF. Prevalence of low serum estradiol levels in male osteoporosis. Osteoporos Int 2000, 11: 697-701.
34. Khosla S, Melton III L, Atkinson E, O`Fallon W. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001, 86: 3555-61.