



Bone mineral density and bone turnover in hyperprolactinaemia of various origins

Gęstość mineralna kości i przebudowa kości w hiperprolaktynemii różnego pochodzenia

Beata Zadrożna-Śliwka, Marek Bolanowski, Marcin Kałużny, Joanna Syrycka

Department of Endocrinology, Diabetology and Isotope Therapy, Wrocław Medical University

Abstract

Introduction: Osteopenia and osteoporosis because of hyperprolactinaemia caused by prolactinoma may be followed by an increased risk of fracture. There are no data on the bone effects of functional hyperprolactinaemia. The aim was to assess the influence of hyperprolactinaemia of various origins on bone turnover and density in different skeletal sites.

Material and methods: The study was carried out in 75 women (aged 30.53 ± 7.8): Group I — 32 women with prolactinoma and Group II — 43 women with functional hyperprolactinaemia. Both groups of patients were subdivided into those with hypogonadism and those with normal gonadal function. The control group consisted of 29 healthy women aged (33.59 ± 4.7). In all subjects PRL and bone turnover markers (BAP, OC, ICTP) were studied. BMD measurements (lumbar spine, forearm, proximal femur and total body) were carried out using DXA.

Results: Higher PRL concentrations were observed in patients than in controls. The values of bone turnover markers (BAP, ICTP) were shown to be higher in patient groups and subgroups than in controls. In patients with prolactinoma lumbar spine BMD was lower than in patients with functional hyperprolactinaemia and controls. Total body BMD was also lower, albeit to a lesser extent.

Conclusions: Hyperprolactinaemia caused by prolactinoma in women influences bone metabolism unfavourably, more by the impact on the activity of bone turnover markers than on BMD. This provides an opportunity for earlier assessment of bone metabolism disturbances before the BMD changes can be observed. Functional hyperprolactinaemia does not determine such a harmful effect on bone metabolism as hyperprolactinemia due to prolactinoma.

(*Pol J Endocrinol* 2007; 58 (2): 116–122)

Key words: prolactinoma, functional hyperprolactinaemia, bone mineral density, bone turnover

Streszczenie

Wstęp: Osteopenia i osteoporoza w wyniku hiperprolaktynemii spowodowanej przez prolaktynoma mogą zwiększać ryzyko złamań. Obecnie brakuje danych w odniesieniu do czynnościowej hiperprolaktynemii. Celem pracy była ocena wpływu hiperprolaktynemii różnego pochodzenia na przebudowę i gęstość kości w różnych miejscach szkieletu.

Materiał i metody: W badaniu uczestniczyło 75 kobiet (wiek $30,53 \pm 7,8$). Do grupy I należały 32 kobiety z prolaktynoma, natomiast do grupy II — 43 kobiety z czynnościową hiperprolaktynemią. Obie grupy podzielono na pacjentki z hipogonadyzmem i prawidłową czynnością gonad. W skład grupy kontrolnej weszło 29 zdrowych kobiet (wiek $33,59 \pm 4,7$). U wszystkich badanych oznaczano stężenie PRL i markerów przebudowy kości (BAP, OC, ICTP). Gęstość mineralna kości (BMD, *bone mineral density*) (kręgosłupa lędźwiowego, przedramienia, bliższej nasady uda i całego ciała) zbadano metodą DXA.

Wyniki: Większe stężenia PRL stwierdzono u pacjentek niż w grupie kontrolnej. Większe wartości markerów przebudowy kości wykazano w grupach i podgrupach pacjentek niż w grupie kontrolnej. U pacjentek z prolaktynoma wartości BMD kręgosłupa lędźwiowego były mniejsze niż u pacjentek z czynnościową hiperprolaktynemią i w grupie kontrolnej. Gęstość mineralna kości całego ciała była również obniżona, ale w mniejszym stopniu.

□ Marek Bolanowski, M.D., Ph.D.
Dept. of Endocrinology, Diabetology and Isotope Therapy
Wybrzeże L. Pasteura 4, 50-367 Wrocław
Poland
phone: 071 784 2740, fax: 071 327 0957
e-mail: bolan@endo.am.wroc.pl

The paper was supported by AM Grant No. 1474

Wnioski: Hiperprolaktynemia, spowodowana przez prolaktynoma u kobiet, wpływa niekorzystnie na metabolizm kostny, bardziej przez działanie na aktywność markerów przebudowy kości niż na BMD, co umożliwiła wczesną ocenę zaburzeń metabolizmu kości, zanim wystąpią zmiany w BMD. Warto wspomnieć, że czynnościowa hiperprolaktynemia nie wywiera tak niekorzystnego wpływu na kości jak prolaktynoma.

(*Endokryol Pol 2007; 58 (2): 116–122*)

Słowa kluczowe: prolaktynoma, czynnościowa hiperprolaktynemia, gęstość kości, przebudowa kości

Introduction

Hyperprolactinaemia is the most common disorder of the hypothalamic-hypophyseal system. It may be caused by prolactin-secreting adenoma (prolactinoma), another pituitary tumour, primary hypothyroidism, renal failure or particular medication. Physiologically, hyperprolactinaemia occurs in pregnancy, during lactation, sexual intercourse, breast nipple irritation, physical exercise, stress or sleep. Spontaneous serum prolactin (PRL) concentration elevations in subjects without pituitary tumour and with no clinical signs of hypothalamic or pituitary stalk disturbances are regarded as functional hyperprolactinaemia [1–3].

Clinical symptoms of hyperprolactinaemia, regardless of its origin, are sterility, menstrual disturbances and galactorrhoea in women and impotence and libido loss in men. Other important metabolic sequelae of persistent hyperprolactinaemia are decreased bone mineral density (BMD) and increased activity of bone turnover markers in both sexes. Data on these harmful bone effects regard patients with prolactin-secreting pituitary tumours, owing to hypogonadism and a decrease in oestrogen secretion [4–6]. Successful treatment of hyperprolactinaemia restores normal bone turnover and bone mass, but these changes occur after some time [7, 8]. There is a significant relative risk of osteoporosis in women harbouring prolactinoma, estimated as factor 4.5. Moreover, untreated hyperprolactinaemia is associated with an increased fracture risk even before the menopause [9, 10].

There is no data in the literature on the influence of functional hyperprolactinaemia on bone metabolism. Moreover, previous studies on bones in hyperprolactinaemia utilised older methods such as computed tomography or photon absorptiometry and the studies were carried out in limited skeletal localisations [11–13]. Dual X-ray absorptiometry (DXA) is a modern densitometric technique and is accepted world-wide as the “gold standard” for BMD studies [14].

The aim of this study was to assess the influence of hyperprolactinaemia of different origins on bone turnover activity and bone mineral density as measured by DXA in various skeletal sites.

Material and methods

Subjects

Seventy five women aged 19–49 years (mean age 30.53 ± 7.8) were recruited for the study from the patients of the Department of Endocrinology, Diabetology and Isotope Therapy, Wrocław Medical University. The subjects were divided into the following three groups: Group I — 32 women with prolactinoma, Group II — 43 women with functional hyperprolactinaemia and Group III — 29 healthy women (control group). Pituitary MRI scans and a PRL stimulation test (0', 60') before and following 10 mg of metoclopramide given orally (the metoclopramide test) were performed, and patients were assigned to the hyperprolactinaemia group on the basis of the results of the scan and the test (Group I — adenoma on MRI and normal PRL response; Group II — no adenoma on MRI and exaggerated PRL response). The exclusion criteria were other diseases or medication known to promote bone loss, treated osteoporosis, chronic liver and renal diseases and neoplasms.

Groups I and II were subdivided according to the presence of hypogonadism assessed on the basis of the presence of oligo- or amenorrhoea. The controls had regular menses, PRL concentration in the normal range, normal gonadal function and no galactorrhoea. The subjects did not differ regarding body weight, height and BMI. Patients with prolactinoma and concomitant hypogonadism, with functional hyperprolactinaemia and with functional hyperprolactinaemia with hypogonadism were younger than the controls ($p = 0.008; 0.007; 0.0002$, respectively). Among the patients with functional hyperprolactinaemia, those with hypogonadism were younger than those with normal gonadal function ($p = 0.02$). The characteristics of the subjects are shown in Table I.

Of 32 patients harbouring prolactinoma, macroadenoma was present in 7 cases (21%) and the remaining 25 had microadenoma. The patients did not differ from the controls regarding diet, smoking habits, caffeine or alcohol ingestion and physical activity. All subjects had normal thyroid, renal and liver function and had received no medication three months prior to or during the study. Analysis of the anamnestic data of the patients

Table I

General characteristics of the group studied (anthropometric parameters and serum PRL concentration)

Tabela I

Ogólna charakterystyka badanych grup (parametry antropometryczne i stężenie prolaktyny [PRL] w surowicy)

Group	Number	Age (years)	Body mass (kg)	Height (cm)	PRL [ng/ml]
I — prolactinoma	32	30.96 ± 8.18	62.53 ± 9.31	165.84 ± 5.39	90.71 ± 81.65*#
Hypogonadism present	14	28.14 ± 7.88*	59.85 ± 7.76	166.07 ± 6.06	119.42 ± 113.85*
Hypogonadism absent	18	33.16 ± 7.93	64.61 ± 10.08	165.66 ± 4.98	69.56 ± 40.68*
II — functional hyperprolactinemia	43	30.20 ± 7.59*	61.25 ± 10.71	164.83 ± 5.33	35.98 ± 27.26*#
Hypogonadism present	27	28.22 ± 6.41* [§]	60.74 ± 11.76	163.74 ± 4.70	37.23 ± 28.85*
Hypogonadism absent	16	33.56 ± 8.42 [§]	62.12 ± 8.97	166.68 ± 5.95	33.74 ± 24.95*
III — control group	29	33.59 ± 4.70	61.70 ± 10.58	163.85 ± 5.37	8.57 ± 4.81

*p < 0.05 in comparison with control group; #p < 0.05 in comparison between groups; §p < 0.05 in comparison between subgroups

showed that there were no differences in mean duration of symptoms or mean period of previous therapy between the groups and subgroups of the patients with hyperprolactinaemia. The protocol of the study was accepted by the local Bioethics Committee, and all the subjects gave their informed consent.

Methods

PRL serum concentrations were studied by the chemiluminescent method using the Immulite 2000-PRL kit (DPC, USA), the normal range for women 1.9–25 ng/ml. The bone turnover markers studied were bone fraction of alkaline phosphatase (BAP) by the thermic method using Enzyline PAL optimise (bioMerieux, France), normal range 100–290 U/l, osteocalcin (OC) by the immunoradiometric method using OSTEO-RIACT (CIS Bio International, France), normal range 7.7–39.4 ng/ml, and C-terminal telopeptide of type I collagen (ICTP) by radioimmunoassay using UNIQ ICTP RIA (Orion Diagnostica, Finland), normal range 2.1–5.6 µg/l.

Bone mineral density (BMD) was studied by DXA using Lunar DPX-plus (Lunar Corp., USA). The following were analysed: the lumbar spine (L₂–L₄) in the anteroposterior projection, the proximal femur (femoral neck, trochanter major, Ward's triangle), the forearm (ultradistal radius, distal 1/3 radius) and the total body. The densitometric results were expressed in measured units (g/cm²) and in standard deviations (SD) with respect to age-matched (Z-score) BMD.

Statistical analysis

Statistical analysis was performed using the STATISTICA software for Windows, version 6.0. Means ± SD were analysed among groups by means of Student's t-test when normally distributed, or by means of Mann-Whitney's ranking sums test when not. As a level of statistical significance a p value of < 0.05 was used.

Results

The highest PRL level was revealed in Group I (prolactinoma), followed by Group II (functional hyperprolactinaemia), both of which had significantly higher levels in statistical terms than the control group (p = 0.000000 for both). Furthermore, the PRL level in Group I was higher than in Group II (p = 0.00002). The PRL levels of the patients with prolactinoma were higher than in the controls and this was true both in the subgroup with hypogonadism (p = 0.000001) and in the subgroup without hypogonadism (normal menses) (p = 0.000000). Similarly, patients with functional hyperprolactinaemia had higher PRL than the controls, both the subgroup with hypogonadism (p = 0.000000) and that without (p = 0.000002) (Table 1, Fig. 1).

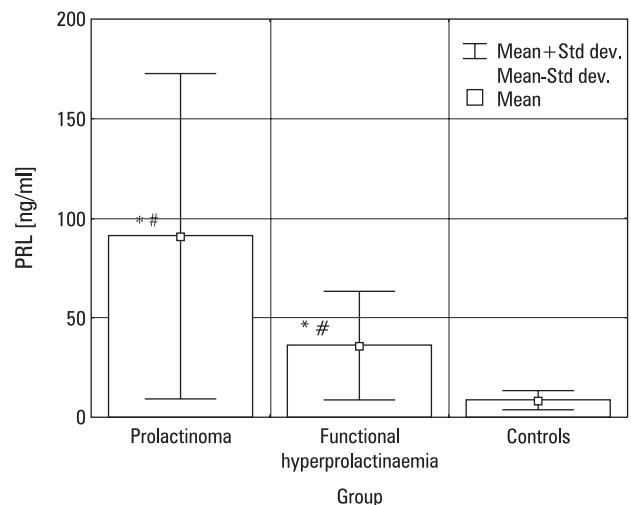


Figure 1. Serum prolactin (PRL) concentration in groups of patients with hyperprolactinaemia and in the control group; *p < 0.05 in comparison with control group; #p < 0.05 in comparison between groups

Rycina 1. Stężenie prolaktyny (PRL) w surowicy w grupach pacjentek z hiperprolaktynemią i w grupie kontrolnej; *p < 0,05 w porównaniu z grupą kontrolną; #p < 0,05 między grupami

Table II

Bone turnover markers: bone fraction of alkaline phosphatase (BAP), osteocalcin (OC) and C-terminal telopeptide of type I collagen (ICTP) in groups and subgroups studied and in the control group

Tabela II

Markery przebudowy kości: frakcja kostna fosfatazy alkalicznej (BAP), osteokalcyna (OC) i C-końcowy telopeptyd kolagenu typu 1 (ICTP) w badanych grupach i podgrupach pacjentek i w grupie kontrolnej

Group	BAP (U/L)	OC [ng/ml]	ICTP [µg/l]
I — prolactinoma	40.89 ± 22.31*	29.68 ± 5.58	3.02 ± 0.86*
Hypogonadism present	42.21 ± 24.18*	29.64 ± 5.83	3.22 ± 0.74*
Hypogonadism absent	39.96 ± 21.60*	29.72 ± 5.55	2.84 ± 0.95*
II — functional hyperprolactinemia	36.63 ± 16.71*	29.57 ± 10.0	2.96 ± 0.91*
Hypogonadism present	39.12 ± 17.61*	31.10 ± 10.46	3.12 ± 1.06*
Hypogonadism absent	31.45 ± 13.90	26.95 ± 8.9	2.69 ± 0.52*
III — control group	28.50 ± 14.25	27.79 ± 5.29	2.25 ± 0.45

*p < 0.05 in comparison with control group

Mean BAP activity was higher in Group I and Group II than in controls ($p = 0.015$; 0.04 , respectively). Among Group I patients, BAP activity was higher than in controls, both in the subgroup with hypogonadism ($p = 0.02$) and in that with normal gonadal function ($p = 0.03$). It was also higher than in controls in hypogonadal patients from Group II ($p = 0.007$). Mean ICTP levels were higher in Groups I and II than in the control group ($p = 0.0005$; 0.0009 respectively). In addition, ICTP levels were higher in all subgroups of patients than in controls ($p = 0.00003$; 0.02 ; 0.0008 ; 0.01 respectively). There were no differences in OC levels between the groups studied and controls (Table II).

Mean lumbar spine BMD values expressed in units and Z-score were lower in Group I than in controls ($p = 0.001$; 0.0008 respectively). Lumbar spine BMD values expressed by Z-score were lower in Group I than in Group II ($p = 0.04$) (Fig. 2). Hypogonadal patients from Group I had a lower lumbar spine BMD assessed by units and Z-score than controls ($p = 0.0002$; 0.0005 respectively). Patients from Group I with normal gonadal function also had lower BMD assessed by units and Z-score than controls ($p = 0.04$; 0.02 , respectively) (Table III).

Mean total body BMD in units and Z-score was lower in Group I than in controls ($p = 0.01$; 0.02 respectively) (Fig. 3). Hypogonadal patients from Group I had lower total body BMD in units and Z-score than controls ($p = 0.01$; 0.04 , respectively). Patients from Group I with normal gonadal function had a lower total body BMD Z-score ($p = 0.04$) than controls (Table III).

Discussion

Persistent hyperprolactinaemia is usually followed by bone metabolism deterioration, causing increased

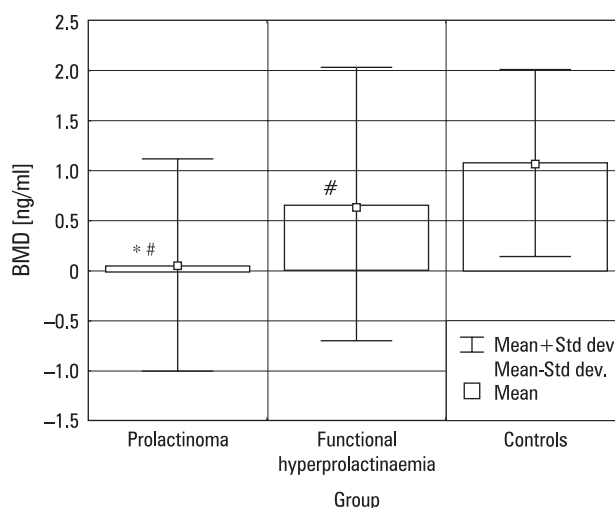


Figure 2. Lumbar spine BMD (Z-score) in groups of patients with hyperprolactinaemia and in the control group; *p < 0.05 in comparison with control group; #p < 0.05 in comparison between groups

Rycina 2. Gęstość mineralna kości (BMD) kręgosłupa lędźwiowego (Z-score) w grupach pacjentek z hiperprolaktynią i w grupie kontrolnej; *p < 0,05 w porównaniu z grupą kontrolną; #p < 0,05 między grupami

bone resorption, bone loss and an increased risk of fractures. These are thought to be consequences of hypogonadotropic hypogonadism caused by hyperprolactinaemia and the direct effect of PRL on the bones [5, 9, 10]. From this point of view, early detection of these hormonal disturbances as the cause of secondary osteoporosis is of great importance for the possible prevention of fractures [1, 15]. To our knowledge, the present study is the first to focus on bone metabolism changes in patients with functional hyperprolactinaemia.

Table III

Lumbar spine (L₂-L₄) and total body BMD expressed in measured units (g/cm²) and Z-score values in groups and subgroups studied and in the control group

Tabela III

Gęstość mineralna kości (BMD) kręgosłupa lędźwiowego (L₂-L₄) i całego ciała wyrażone w jednostkach pomiaru (g/cm²) i wartościach Z-score w grupach i podgrupach pacjentek i w grupie kontrolnej

Group	L ₂ -L ₄ BMD [g/cm ²]	L ₂ -L ₄ Z-score (SD)	Total body BMD [g/cm ²]	Total body Z-score (SD)
I — prolactinoma	1.190 ± 0.10*	0.056 ± 1.06*#	1.107 ± 0.07*	-0.096 ± 0.81*
Hypogonadism present	1.148 ± 0.16*	-0.235 ± 1.04*	1.098 ± 0.07*	-0.095 ± 0.79*
Hypogonadism absent	1.232 ± 0.15*	0.295 ± 1.04*	1.115 ± 0.07	-0.098 ± 0.85*
II — functional hyperprolactinaemia	1.263 ± 0.19	0.662 ± 1.36#	1.127 ± 0.08	0.221 ± 0.80
Hypogonadism present	1.246 ± 0.17	0.531 ± 1.38	1.128 ± 0.08	0.230 ± 0.78
Hypogonadism absent	1.291 ± 0.17	0.883 ± 1.35	1.125 ± 0.08	0.204 ± 0.88
III — control group	1.320 ± 0.16	1.073 ± 0.93	1.153 ± 0.05	0.421 ± 0.59

*p < 0.05 in comparison with control group; #p < 0.05 in comparison between groups

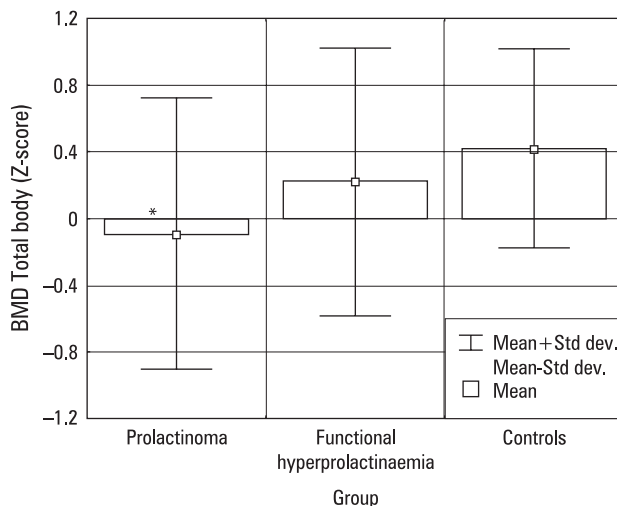


Figure 3. Total body BMD (Z-score) in groups of patients with hyperprolactinaemia and in the control group; *p < 0.05 in comparison with control group

Rycina 3. Gęstość mineralna kości (BMD) całego ciała (Z-score) w grupach pacjentek z hiperprolaktynemią i w grupie kontrolnej; *p < 0,05 w porównaniu z grupą kontrolną; #p < 0,05 między grupami

We observed higher PRL levels in our patients with prolactinoma than in patients with functional hyperprolactinaemia and the control group. PRL levels in functional hyperprolactinaemia were also higher than in controls. These differences from the controls were significant regardless of gonadal dysfunction in hyperprolactinaemic patients, but the higher PRL concentrations were in hypogonadal patients. These observations confirm the association of the level of hyperprolactinaemia with the presence of prolactinoma and disturbances of gonadal function [1, 5].

In the current study two bone formation markers (BAP and OC) and one resorption marker (ICTP) were studied. The levels of BAP and ICTP were observed to be higher in the patients with prolactinoma and functional hyperprolactinaemia than in the control group. It is difficult to explain the absence of changes in OC levels in our groups, current data being supported by other observations of higher bone turnover in hyperprolactinaemia followed by increased bone loss later on [7, 8]. The bone turnover processes are coupled to each other, so that the initial increase in the resorption is associated with an increase in bone formation some time later. The consequences of the increased bone turnover because of untreated hyperprolactinaemia are a decrease in BMD and an increase in fracture risk [10, 16]. In some studies an increase in bone resorption and formation activity has been observed in hyperprolactinaemia, while there has been no change in OC levels, as in our results. Others point to decreased formation together with increased bone resorption, both of which normalised during therapy [7, 17-19]. In another work the therapy normalised decreased bone formation but bone resorption remained at the higher level [8]. In the present study the acute effect of current therapy was not analysed. This will be possible in the future, following repeated measurements after successful PRL-normalising therapy. Some studies show higher values for bone turnover markers in hyperprolactinaemic patients with hypogonadism [18]. No differences were shown between subgroups in terms of the gonadal status of our patients. This observation may suggest the utility of bone turnover markers in the early diagnostics of bone metabolism deterioration because of hyperprolactinaemia before the BMD changes occur [8].

We have shown lumbar spine BMD to be lower in female patients harbouring prolactinoma than in controls. BMD values were also lower in patients with prolactinoma than in those with functional hyperprolactinaemia. Both hypogonadal patients with prolactinoma and those with normal gonadal function had lower lumbar spine BMD than the controls. The lumbar spine contains mainly trabecular bone, and this bone is very sensitive to metabolic influences such as sex hormone deficiency. Our patients were at reproductive age, and the decrease in Z-score is the most reliable marker of bone loss in premenopausal subjects [14]. This indicates greater bone deterioration in prolactinoma than in functional hyperprolactinaemia. Differences in age between the groups studied had no significant influence on the BMD results since they were present when expressed in the Z-scores, which were also age-dependent.

No significant differences in BMD were observed between the hyperprolactinaemic patients and controls in the proximal femur and forearm. Total body densitometry revealed lower BMD values in patients with prolactinoma than in controls. The lowest values were shown in the subgroup with hypogonadism. Total body densitometry reflects the cortical bone and this measurement has great value in children and adolescents [14], while being of less value in adults of reproductive age, as our subjects were.

We observed a loss of BMD of about 11% within the lumbar spine in patients with prolactinoma, and bone loss of about 4% in the total body scans. The difference in bone loss between prolactinoma and functional hyperprolactinaemia was about 7%. The deterioration in trabecular bone, although not great, may lead to fractures in the future. Other studies showed similar, or even greater, bone loss in hyperprolactinaemic patients, mainly regarding trabecular bone [13, 20, 21]. Schlechte et al. showed a decrease in vertebral BMD in hyperprolactinaemia as compared to controls but not in the forearm (cortical bone) [13]. These data support our observation that hyperprolactinaemia has a greater influence on the trabecular bone. In another study amenorrhoeic patients with hyperprolactinaemia showed BMD 17% lower in the cortical bone but 15–35% lower in the trabecular bone [22]. Some studies have indicated that regularly menstruating women have higher lumbar spine BMD than those with menstrual disturbances [23–25]. Kayath et al. revealed a positive correlation between years of hypogonadism and the extent of bone loss within the spine and femoral neck [12].

The current study is one of the first to utilise the DXA method to assess BMD in all possible measurement sites, previous studies having been limited to the spine and forearm [13, 25], spine and femoral neck [7, 10]

or spine only [20, 26]. Apart from DXA, other techniques such as quantitative computed tomography [13, 15, 25], single-photon absorptiometry [17, 25] and quantitative ultrasound [9] have been used.

We did not identify any differences in BMD and bone turnover between patients who had been treated in the past and those who had not. The data from the literature show that medical therapy of hyperprolactinaemia does not completely normalise bone metabolism. The therapy increases BMD but does not restore normal BMD, even several years following normalisation of gonadal function [20, 27, 28]. The greatest BMD loss in untreated hyperprolactinaemia occurs within the initial two years of menstrual disturbance [17, 25]. Patients with gonadal function restored by therapy had slightly higher BMD values than those untreated yet significantly lower than controls [28]. The greatest increase in BMD was recorded following 6–12 months of therapy [7, 20, 27], but even 18 months of therapy did not restore normal BMD and bone turnover, regardless of gonadal function normalisation [8].

Conclusions

1. Hyperprolactinaemia caused by prolactinoma in women unfavourably influences bone metabolism more by the impact on the activity of bone turnover markers than on BMD. It gives an opportunity for earlier assessment of bone deterioration before BMD changes occur.
2. Functional hyperprolactinaemia does not determine such a harmful effect on bone metabolism as hyperprolactinaemia due to prolactinoma.

References

1. Biller BMK, Luciano A. Guidelines for the diagnosis and treatment of hyperprolactinemia. *J Reprod Med* 1999; 44: 1075–1084.
2. Ciccarelli A, Daly F, Beckers A. The epidemiology of prolactinomas. *Pituitary* 2005; 8: 3–6.
3. Mah PM, Webster J. Hyperprolactinaemia: etiology, diagnosis, and management. *Semin Reprod Med* 2002; 20: 365–374.
4. Kałużny M, Bolanowski M. Hiperprolaktynemia: przyczyny, objawy kliniczne i możliwości terapeutyczne. *Post Hig Med Dośw (online)* 2005; 59: 20–27.
5. Luciano AA. Clinical presentation of hyperprolactinemia. *J Reprod Med* 1999; 44: 1085–1090.
6. Bolanowski M, Kałużny M. Zaburzenia metabolizmu i gęstości kości w hiperprolaktynemii. *Terapia* 2005; 2: 15–17.
7. Colao A, Di Somma C, Loche S et al. Prolactinomas in adolescents: persistent bone loss after 2 years of prolactin normalization. *Clin Endocrinol* 2000; 52: 319–327.
8. 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: 807–813.
9. Vartej P, Poiana C, Vartej I. Effects of hyperprolactinaemia on osteoporotic fracture risk in premenopausal women. *Gynecol Endocrinol* 2001; 15: 43–47.

10. Vestergaard P, Jorgensen JOL, Hagen C et al. Fracture risk increased in patients with GH deficiency or untreated prolactinomas — a case-control study. *Clin Endocrinol* 2002; 56: 159–167.
11. Klibanski A, Neer RM, Beitins IZ et al. Decreased bone density in hyperprolactinemic women. *N Engl J Med* 1980; 303: 1511–1514.
12. Kayath MJ, Lengyel AM, Vieira JG. Prevalence and magnitude of osteopenia in patients with prolactinoma. *Braz J Med Biol Res* 1993; 26: 933–941.
13. Schlechte J, El-Khoury G, Kathol M et al. Forearm and vertebral bone mineral in treated and untreated hyperprolactinemic amenorrhea. *J Clin Endocrinol Metab* 1987; 64: 1021–1026.
14. Lewiecki EM, Kendler DL, Kiebzak GM et al. Special report on the official positions of the International Society for Clinical Densitometry. *Osteoporos Int* 2004; 15: 779–784.
15. Fitzpatrick LA. Secondary causes of osteoporosis. *Mayo Clin Proc* 2002; 77: 453–468.
16. Looker AC, Bauer DC, Chesnut CH et al. Clinical use of biochemical markers of bone remodeling: current status and future directions. *Osteoporos Int* 2000; 11: 467–480.
17. Schlechte J, Walkner L, Kathol M. A longitudinal analysis of premenopausal bone loss in healthy women and women with hyperprolactinaemia. *J Clin Endocrinol Metab* 1992; 75: 698–703.
18. Shaaraway M, El-Dawakhly AS, Mosaad M et al. Biomarkers of bone turnover and bone mineral density in hyperprolactinemic amenorrheic women. *Clin Chem Lab Med* 1999; 37: 433–438.
19. Sartorio A, Conti A, Ambrosi B et al. Osteocalcin levels of patients with microprolactinoma before and during medical treatment. *J Endocrinol Invest* 1990; 13: 419–422.
20. Biller BMK, Baum HBA, Rosenthal DI et al. Progressive trabecular osteopenia in women with hyperprolactinemic amenorrhea. *J Clin Endocrinol Metab* 1992; 75: 692–697.
21. Koppelman MC, Kurtz DW, Morrish KA et al. Vertebral body bone mineral content in hyperprolactinemic women. *J Clin Endocrinol Metab* 1984; 59: 1050–1053.
22. Miller KK, Klibanski A. Amenorrheic bone loss. *J Clin Endocrinol Metab* 1999; 84: 1775–1783.
23. Drinkwater BL, Brummer B, Chestnut CH 3 III. Menstrual history as a determinant of current bone density in young athletes. *JAMA* 1990; 263: 545–548.
24. Ciccarelli E, Savino L, Carlevatto V et al. Vertebral bone density in non-amenorrhoeic hyperprolactinemic women. *Clin Endocrinol* 1988; 28: 1–6.
25. Klibanski A, Biller BM, Rosenthal DI et al. Effects of prolactin and estrogen deficiency in amenorrheic bone loss. *J Clin Endocrinol Metab* 1988; 67: 124–130.
26. Matsuyama J, Eshima N, Fukunaga T et al. Various risk of osteoporosis in patients with pituitary adenomas. *J Bone Miner Metab* 2003; 21: 91–97.
27. Klibanski A, Greenspan SL. Increase in bone mass after treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1986; 315: 542–546.
28. Schlechte JA. Clinical impact of hyperprolactinaemia. *Baillieres Clin Endocrinol Metab* 1995; 9: 359–366.