ORIGINAL ARTICLE

The role of cyclase activating (CAP) and cyclase inhibiting (CIP) parathormone fractions in the assessment of bone metabolism disturbances in women with hyperprolactinemia of various origin

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Abstract

OBJECTIVES: Hyperprolactinemia could be one of possible causes of bone loss. The reason is thought to be connected with hypogonadism due to PRL excess and the role of other hormones like PTH and PTH-rP. There is no data on the influence of PTH fractions (CAP and CIP) on bone turnover and density in hyperprolactinemia. The aim of the study was to assess the influence of PTH and its fractions on bone metabolism in hyperprolactinemia of various origin.

MATERIAL AND METHODS: The study was carried out in 75 women. Group I consisted of 32 women with prolactinoma, group II consisted of 43 women with functional hyperprolactinemia. Both groups were subdivided in patients with hypogonadism and normal gonadal function. The control group consisted of 29 healthy women. In all subjects PRL, PTH and its fractions (CAP, CIP), and bone turnover markers (BAP, ICTP) were studied. BMD measurement was carried out using DXA.

RESULTS: In patients with functional hyperprolactinemia i-PTH and CAP levels were lower than in controls. CIP concentrations were lower in patients than in controls. CAP/CIP ratio was higher in patients with prolactinoma than in patients with functional hyperprolactinemia and controls. Higher values of bone turnover markers (BAP, ICTP) in patients groups and subgroups were shown as compared to controls. Some correlations between PTH and its fractions, and BMD and bone turnover were observed.

CONCLUSIONS: There is no direct benefit from the assessment of parathormone fractions and CAP/CIP ratio in the prognosis of bone metabolism changes in hyperprolactinemia of various origin.

Abbreviations:

BAP	– bone fraction of alkaline phosphatase
BMD	– bone mineral density
BMI	– body mass index
CAP	– cyclase activating parathormone
CIP	– cyclase inhibiting parathormone
DHEA-S	– dehydroepiandrosterone sulfate
DXA	– dual-energy X-ray absorptiometry
ICTP	– C-terminal telopeptide of type 1 collagen
i-PTH	– intact parathormone
MRI	– magnetic resonance imaging
PRL	– prolactin
PTH	– parathyroid hormone, parathormone
PTH-rP	– parathormone-related peptide
SHBG	– sex hormone binding globuline

INTRODUCTION

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. It occurs most commonly in women from 20 to 50 years old. Various physiological and pathological processes increase prolactin (PRL) secretion (Bob *et al.* 2007; Karasek *et al*. 2006). The causes of hyperprolactinemia include also PRL secreting pituitary adenoma – prolactinoma (Ciccarelli *et al.* 2005). Other cause is spontaneous serum PRL concentration elevations in subjects without pituitary tumor, with no clinical signs of hypothalamic or pituitary stalk disturbances, so called functional hyperprolactinemia (Kałużny & Bolanowski, 2005).

Hyperprolactinemic women may present with menstrual disturbances and galactorrhea, the important metabolic consequences of chronic hyperprolactinemia is decreased bone mineral density (BMD). The reason of above mentioned is gonadal dysfunction, although the direct PRL influence on BMD changes is possible, too. The role of other hormones (estradiol, testosterone, DHEA-S, SHBG, progesterone, PTH and PTH-rP) on BMD changes is postulated (Colao *et al.* 2000; Di Somma *et al*. 1998; Zadrożna *et al*. 2007). The problem is very important, since untreated hyperprolactinemia is associated with increased fracture risk even before the menopause (Vartej *et al*. 2001; Vestergaard *et al*. 2002). Till now, there is no data about the role of parathormone fractions (CAP and CIP) in hyperprolactinemia.

PTH is the calcitropic hormone, which has both catabolic and anabolic effects on the bones. Serum concentrations of its C- and N-terminal fragments are controlled by parathyroid glands on the secretory level as well as by hepatic catabolism and kidney filtration (Reichel *et al*. 2003). Up to date, contribution of particular fractions of PTH in bone metabolism were monitored in patients with chronic renal insufficiency. However, in these patients the concentrations of i-PTH were not representative for presence and severity of bone metabolism disturbances due to hyperparathyroidism (Gao *et al*. 2001). It was attributed to disorder of ratio between the fragment composed of 84 aminoacids (1-84 PTH), called the adenyl cyclase activating (CAP) PTH, responsible for calcium concentration and bone turnover increase, and the fragment devoid of the first 6 aminoacids (7-84 PTH), known as the cyclase inhibiting (CIP) PTH, which acts in the opposite way (Lepage *et al.* 1998; Slatopolsky *et al.* 2000). In some papers it was suggested that the CAP/CIP ratio is sufficient precise measure of the bone turnover, what in practice enables non-invasive assessment of the bone metabolism. Although, there are also some reports, which denied the above findings (Coen *et al*. 2002; Reichel *et al*. 2003), as well. Presence of a relation between PTH (in particular the whole PTH) and markers of the bone balance was demonstrated. Such relation between the markers and the CAP/CIP ratio was not found (Nakanishi *et al.* 2001; Reichel *et al*. 2003).

To our best knowledge, the present study is the first assessing the influence of CAP and CIP on bone metabolism changes in hyperprolactinemia.

MATERIAL AND METHODS

Subjects

Seventy five women aged 19–49 yr (mean 30.53±7.8) were studied. The subjects were divided in three groups: I – 32 women with prolactinoma, II – 43 women with functional hyperprolactinemia, and III – 29 healthy women (control group). The patients were assigned into groups depending on results of the PRL response following oral administration of 10 mg of metoclopramide (metoclopramide test) and pituitary MRI scans (Group I – adenoma on MRI, normal PRL response; Group II – no adenoma on MRI, exaggerated PRL response). Exclusion criteria were: diseases or medication which promote bone loss, treated osteoporosis, chronic liver and renal diseases, neoplasms.

The groups with hyperprolactinemia were subdivided according to the presence of hypogonadism (oligo- or amenorrhea). The controls had regular menses, normal gonadal function, no galactorhoea present and PRL concentration within the normal range. The subjects did not differ regarding body weight, height and BMI. Patients with prolactinoma and concomitant hypogonadism, patients with functional hyperprolactinemia, and patients with functional hyperprolactinemia with hypogonadism were younger from the controls (p=0.008; 0.007; 0.0002, respectively). Among the patients with functional hyperprolactinemia, those with hypogonadism were younger than those with normal gonadal function (p=0.02). Characteristics of the subjects is shown in Table 1.

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. They had no medication 3 months prior to and during the study. All women were recruited from the patients of the Department of Endocrinology, Diabetology and Isotope Therapy, Wroclaw Medical University. The protocol of the study was accepted by

Table 1. General characteristics of groups and subgroups studied and the control group.

Group	Number	Age (years)	BMI (kg/m^2)	Adipose tissue (%)
I – prolactinoma	**32**	30.96 ± 8.18	22.73 ± 3.28	31.82 ± 7.06
hypogonadism present	14	28.14 ± 7.88 *	21.65 ± 2.09	31.04 ± 3.74
hypogonadism absent	18	33.16 ± 7.93	23.57 ± 3.82	32.50 ± 9.12
II – functional hyperprolactinemia	**43**	30.20 ± 7.59 *	22.53 ± 3.8	32.72 ± 8.25
hypogonadism present	27	28.22 ± 6.41 *$	22.65 ± 4.26	33.10 ± 8.77
hypogonadism absent	16	33.56 ± 8.42 $	22.33 ± 3.0	31.99 ± 7.39
III - control group	**29**	33.59 ± 4.70	22.98 ± 3.78	34.23 ± 8.39

***** $p < 0,05$ in comparison with control group
$ $p < 0,05$ in comparison between subgroups

the local Bioethics Committee, and all of subjects gave their informed consent.

Methods

PRL serum concentration was studied by chemiluminescent method using Immulite 2000-PRL kit (DPC, USA). Normal range for women 1.9–25 ng/ml. Metoclopramide test – assessment of serum concentration of prolactin before and following (0', 60') 10 mg of metoclopramide given orally. Whole PTH (1-84) serum concentration and total intact PTH (1-84 PTH and 7-84 PTH) was studied by immunoradiometric method (IRMA) using Duo PTH Kit (Scantibodies Laboratory, USA). Normal ranges: whole PTH (CAP) 5–39 pg/ml, total intact PTH 14–66 pg/ml. Serum concentration of CIP (7-84) was the result of a subtraction serum concentration of intact PTH and whole PTH (1-84). Estradiol (E_2) and sex hormone binding globuline (SHBG) were assessed by chemiluminescent method using Immulite 2000-Estradiol and Immulite 2000-SHBG kits (DPC, USA). Among bone turnover markers, bone fraction of alkaline phosphatase (BAP) by thermic method using Enzyline PAL optimise (bioMerieux, France), normal range 100–290 U/l 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, were studied. Inorganic phosphate was studied using PhosphoreUV kit (bioMerieux, France). Bone mineral density (BMD) was studied by DXA using Lunar DPX-plus (Lunar Corp., USA). There were analyzed: lumbar spine (L_2-L_4) in the antero-posterior projection, proximal femur (femoral neck, trochanter major, Ward's triangle), forearm (ultradistal radius, distal 1/3 radius) and total body. Total body DXA scans measured percentage of adipose tissue.

Statistical analysis

Statistical analysis was done using computer program Statistica for Windows, version 6,0. Means ± SD were analyzed among groups by means Student's t-test when normally distributed, or by means Mann-Whitney's ranking sums test when not. Correlation analysis was performer using Spearman's test. As a level of statistical significance p value < 0.05 was used.

RESULTS

The highest PRL level was shown in Group I (prolactinoma), then in Group II (functional hyperprolactinemia), they both were statistically significantly higher than in control group (p=0.000000 for both). PRL level in Group I was higher than in Group II (p=0.00002), too. Among the patients with prolactinoma, their PRL levels were higher than in controls both in the subgroup with hypogonadism (p=0.000001) as in the subgroup without hypogonadism (normal menses)(p=0.000000). Similarly, patients with functional hyperprolactinemia had higher PRL than the controls, both the subgroup with hypogonadism (p=0.000000) and without hypogonadism (p=0.000002) (Table 2, Figure 1).

Mean i-PTH level was statistically significantly lower in Group II than in control group (p=0.01). Among the patients with hypogonadism in both Group I and II, i-PTH level was statistically significantly lower than in controls (p=0.02, p=0.025) (Table 2). Mean CAP level was statistically significantly lower in Group II than in control group (p=0.04). Patients from Group I with hypogonadism had lower CAP level than patients from subgroup with normal gonadal function (p=0.015) (Table 2). Among Group I and II of patients, mean CIP level was statistically significantly lower than in controls (p=0.006; 0.02, respectively). There were no differences in CIP levels between Group I and II. Patients in both subgroups with hypogonadism had statistically significantly lower CIP than the controls (p=0.008; 0.008, respectively) (Table 2).

Mean CAP/CIP ratio was statistically significantly higher in Group I than in controls (p=0.01), and than in Group II (p=0.04). Among Group I patients, CAP/CIP ratio was lower in subgroup with hypogonadism than in those with normal gonadal function (p=0.009). Patients from Group I with normal gonadal function had CAP/CIP ratio statistically significantly higher than controls (p=0.00008) (Table 2, Figure 2).

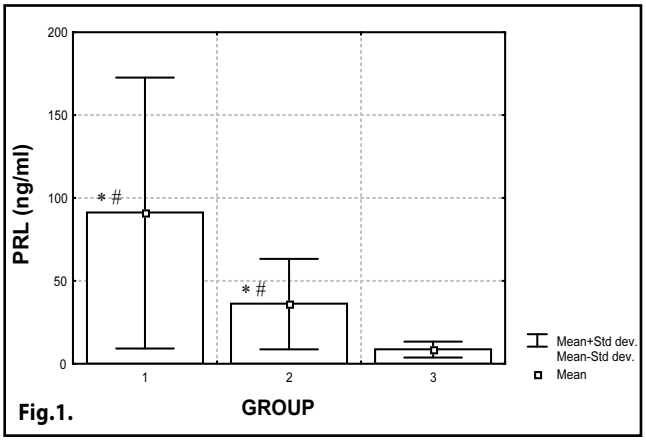
Table 2. Serum concentration of PRL, i-PTH, CAP, CIP, CAP/CIP in groups and subgroups studied and in the control group.

Group	PRL (ng/ml)	**i-PTH** (pg/ml)	CAP (pg/ml)	CIP (pg/ml)	CAP/CIP
I – prolactinoma	90.71 ± 81.65 *#	35.62 ± 16.53	23.41 ± 9.90	12.21 ± 8.00 *	2.36 ± 1.34 * #
hypogonadism present	119.42 ± 113.85 *	30.25 ± 8.91 *	18.69 ± 5.78 $	11.56 ± 3.73 *	1.67 ± 0.43 $
hypogonadism absent	69.56 ± 40.68 *	40.28 ± 20.22	27.50 ± 11.03 $	12.77 ± 10.53	2.95 ± 1.58 * $
II – functional hyperprolactinemia	35.98 ± 27.26 *#	32.32 ± 10.13 *	19.75 ± 6.76 *	12.56 ± 5.47 *	2.03 ± 1.70 #
hypogonadism present	37.23 ± 28.85 *	31.82 ± 11.24 *	20.21 ± 7.68	11.60 ± 5.06 *	1.96 ± 0.97
hypogonadism absent	33.74 ± 24.95 *	33.06 ± 8.54	19.06 ± 5.28	14.00 ± 5.95	2.14 ± 2.47
III - control group	8.57 ± 4.81	40.71 ± 13.11	24.34 ± 8.73	16.37 ± 5.27	1.52 ± 0.43

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

Table 3. Correlations between concentrations of i-PTH and its fractions and other parameters studied in patients with prolactinoma.

	Parameters studied	Spearman correlation coefficient	p
i-PTH	CAP	0.91	**0.000000**
	CIP	0.72	**0.00001**
	L_2-L_4 BMD	0.38	**0.04**
CAP	CIP	0.47	**0.01**
	BAP	0.40	**0.04**
	L_2-L_4 BMD	0.38	**0.04**
CIP	CAP/CIP	–0.69	**0.00004**
CAP/CIP	Estradiol	0.43	**0.02**
	SHBG	0.38	**0.04**



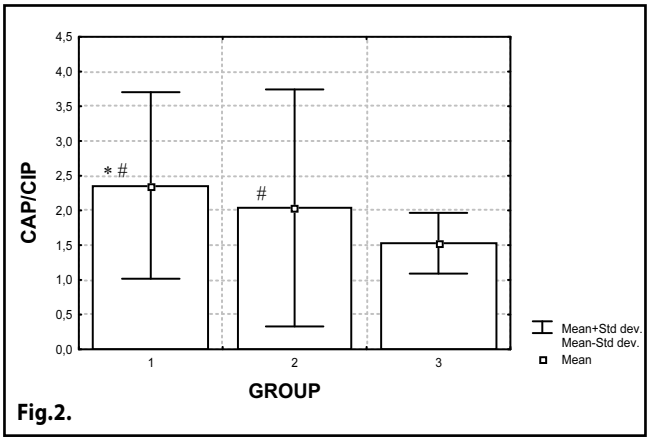


Figure 1. Serum prolactin (PRL) concentration in groups of patients with hyperprolactinemia and in the control group.
1 – prolactinoma; 2 – functional hyperprolactinemia;
3 – control group
* $p < 0.05$ in comparison with control group
\# $p < 0.05$ in comparison between groups

Figure 2. Serum CAP/CIP in groups of patients with hyperprolactinemia and in the control group.
1 – prolactinoma; 2 – functional hyperprolactinemia
3 – control group
* $p < 0.05$ in comparison with control group
\# $p < 0.05$ in comparison between groups

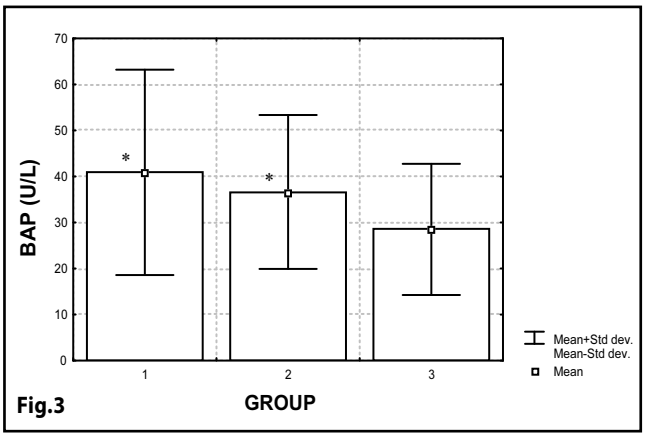


Figure 3. Serum bone fraction of alkaline phosphatase (BAP) concentration in groups of patients with hyperprolactinemia and in the control group.
1 – prolactinoma; 2 – functional hyperprolactinemia;
3 – control group
* $p < 0.05$ in comparison with control group

Table 4. Correlations between concentrations of i-PTH and its fractions and other parameters studied in patients with functional hyperprolactinemia.

	Parameters studied	Spearman correlation coefficient	p
i-PTH	CAP	0.82	**0.000000**
	CIP	0.79	**0.000000**
	ICTP	–0.34	**0.04**
	ultradistal radius BMD	0.45	**0.007**
	percent of adipose tissue	0.34	**0.04**
CAP	CIP	0.36	**0.04**
	phosphate	–0.46	**0.005**
	ICTP	–0.37	**0.03**
	L_2-L_4 BMD	0.39	**0.02**
	femoral neck BMD	0.43	**0.009**
	ultradistal radius BMD	0.47	**0.004**
	total body BMD	0.46	**0.006**
	percent of adipose tissue	0.38	**0.03**
CIP	CAP/CIP	–0.61	**0.0001**
	ultradistal radius BMD	0.36	**0.03**
CAP/CIP	Ward's triangle BMD	0.35	**0.04**
	total body BMD	0.34	**0.04**

Mean activity of BAP was higher in Group I and Group II in comparison with controls (p=0.015; 0.04, respectively) (Figure 3). Similarly, mean ICTP levels were higher in Group I and Group II in comparison with control group (not shown).

In patients from Group I there was statistically significant positive correlation between i-PTH and CAP on one side and lumbar spine BMD on the other side. There was positive correlation between CAP and BAP, CAP/CIP ratio and E_2 and SHBG concentrations, as well (Table 3). In Group II patients there was positive correlation between i-PTH and ultradistal forearm BMD and percent of body fat, and negative correlations between i-PTH and ICTP and phosphate levels. Among this group there was statistically significant positive correlation between CAP and BMD within lumbar spine, femoral neck, ultradistal forearm, and total body, and percent of body fat. CIP correlated positively with ultradistal forearm BMD, and CAP/CIP positively with both Ward's triangle and total body BMD (Table 4). There were obvious correlations among PTH and its fractions in both groups, of course.

DISCUSSION

An important metabolic consequence of chronic hyperprolactinemia is bone loss, BMD decrease and increased risk of fractures. They are thought to be associated with influence of many hormones like PRL, sex steroids, DHEA-S, SHBG, PTH and PTH-rP (Colao *et al.* 2000; Di Somma *et al.* 1998). This is the first study assessing the influence of CAP and CIP on bone metabolism changes in hyperprolactinemia.

Secretion of PTH is controlled by calcium concentration in a negative feedback, an additional modulating role play vitamin D and phosphate levels, and catabolic transformation in the liver and kidneys. It was found that low level of calcium stimulates secretion of 1-84 PTH, whereas high level of calcium – the 7-84 PTH, what influences the CAP/CIP ratio. So, small CAP/CIP ratio is characteristic for low activity of parathyroid glands (Reichel *et al.* 2003). According to various reports, PRL may have different effects on PTH concentration (Colao *et al.* 2000; Fiore *et al.* 1984). It was found in the present study that in groups of women with hyperprolactinemia the i-PTH concentrations were maintained within the range of normal values, without any significant differences. Lower concentrations of i-PTH in women with functional hyperprolactinemia as compared to the control group were noticed. Lower concentration of i-PTH was found in women with prolactinoma and hypogonadism as well as in women with functional hyperprolactinemia and hypogonadism, than in patients from the control group. In this study, there was no correlation between PRL and i-PTH concentrations both in the group of women with prolactinoma and in the functional hyperprolactinemia, what agrees with other published results (Fiore *et al.* 1984).

It was found in the present study that higher concentrations of CAP occurred in the control group, as compared to these in the groups of patients with hyperprolactinemia, however statistically significant differences were observed between women with functional hyperprolactinemia and the control group, only. In the group of patients with prolactinoma, gonadal

function effect on the concentration of CAP was noticed; patients without hypogonadism showed higher CAP values. Moreover, significantly higher concentrations of CIP were found in the control group, as compared to these in any of the groups examined. In both subgroups of women with hypogonadism statistically significantly lower CIP values were noticed, as compared to these of the control group.

In the group of patients some correlations between concentration of i-PTH and concentrations of CAP and CIP, as well as between CAP and CIP and their ratio were found. They seems to be obvious, because the intact PTH includes both the (1-84) PTH, i.e. CAP, and its fragment – the (7-84) PTH, i.e. CIP molecules (Lepage *et al*. 1998; Slatopolsky *et al.* 2000). Interesting is the fact, that there is no correlation between concentration of CAP and the CAP/CIP ratio in the women with adenoma, what may be the evidence for dominating role of improper secretion of the CIP fraction, what influences the ratio. In the references available, no information about possible other mechanisms of the control of the secretion of both fractions of PTH was found. Since the women examined had normal kidney and liver function, the conclusion may be drawn that correlation between i-PTH and its fractions confirm the fact of related secretion CAP and CIP by the parathyroid glands (Gao *et al*. 2001). The highest CAP/CIP ratio was found in women with prolactinoma, whereas the smallest – in the control group. The differences were statistically significant. In the group of the patients with adenoma the CAP/CIP ratio was higher than in the group of patients with functional hyperprolactinemia. In the group of women with prolactinoma effect of hypogonadism on the CAP/CIP ratio was more pronounced. The ratio was statistically significantly lower in women with hypogonadism, as compared to the group of women with normal gonadal function. It is mainly the result of lower concentration of CAP. There are no reports on advantage of determination of active form of PTH (CAP) over determination of i-PTH, or data on shares of particular PTH fractions, or on the role of the CAP/PIP ratio in evaluation of bone changes in hyperprolactinemia. It was found in this study that the maximum CAP/CIP ratio had patients with prolactinoma, at lower (however within the standard range) concentration of calcium – statistically insignificant, as compared to concentrations showed in other groups. Basing on the reports, that the ratio may be the measure of the bone turnover, and that ratios > 1 denote high bone turnover and are significantly above ratios in the control group, the hypothesis may be presented that it is the cause of higher bone loss in women with hyperprolactinemia in course of prolactinoma, as compared to the group of healthy women, however it is not indicative in case of women with functional hyperprolactinemia. Apart from above, the healthy women had the CAP/CIP ratios above one, as well.

In some studies the correlation between bone turnover markers and particular PTH fractions was examined. It was shown, that there is a strong correlation between PTH (and particularly the whole PTH) and the bone turnover markers, but no relation between the markers and the CAP/CIP ratio was found (Nakanishi *et al*. 2001; Reichel *et al*. 2003). In present study, higher levels of BAP and ICTP were observed in our patients with prolactinoma and functional hyperprolactinemia than in the controls. In the group with prolactinoma, positive correlation between concentrations of CAP and BAP was noticed. On the other hand, in the group with functional hyperprolactinemia both concentrations of i-PTH and CAP showed negative correlation with ICTP. It may be the evidence of anabolic effects of PTH in this group, because ITCP is the bone resorption marker. It is an original finding, not confirmed by other available papers, which suggest relations between i-PTH and BAP and OC, only (Reichel *et al*. 2003). In the groups of patients examined, correlation of PTH or its fractions concentrations with OC was not found, in spite of the fact that some researchers suggested that such correlations exist (Reichel *et al*. 2003). No correlation between values of the CAP/CIP ratio and the bone turnover markers were noticed in our study, as it was shown by other authors (Nakanishi *et al*. 2001; Tsuchida *et al.* 2006). There were some attempts to find a relation between changes of bone density in women with hyperprolactinemia and effects of PTH-rP. PTH-rP may be secreted simultaneously with PRL by prolactin-secreting adenoma or as the result of stimulation by PRL (Kovacs & Chik, 1995). In our study, concentrations of PTH-rP were not assessed, therefore the problem can not be discussed here.

We have shown lower lumbar spine BMD in female patients harboring prolactinoma than in controls. BMD values in patients with prolactinoma were lower than in functional hyperprolactinemia, too. Both hypogonadal patients with prolactinoma and those with normal gonadal function had lower lumbar spine BMD than the controls. Lumbar spine contains mainly from trabecular bone (Zadrożna *et al*. 2007). This shows greater bone deterioration while prolactinoma, than functional hyperprolactinemia. Total body densitometry revealed lower BMD values in patients with prolactinoma than in controls. The lowest values were shown in the subgroup with hypogonadism. The total body densitometry reflects the cortical bone, this measurement has a great value in children and adolescents (Zadrożna *et al*. 2007). It is of less value in the adults in the reproductive ages, as our subjects were. Similarly, changes in BMD were related to gonadal status and some cytokines in patients with acromegaly (Bolanowski *et al*. 2006).

An interesting observation is the existence of relations between i-PTH and BMD of various parts of the skeleton in particular groups of patients. In this paper, a positive correlations between concentration of i-PTH (and CAP) and lumbar spine BMD in the group of

women with prolactinoma as well as positive correlations between concentration of i-PTH and ultradistal radius BMD in the group of women with functional hyperprolactinemia (in the both cases predominance of the trabecular bone in these locations) were found. Until now it was commonly believed that PTH is a peptide stimulating resorption of bone tissue and progressive destruction of the skeleton (Strewler, 2001). Only recently its anabolic effect was documented; as the consequence, new therapeutical methods for treatment of osteoporosis were elaborated (Neer *et al*. 2001). Share of PTH in changes of BMD in hyperprolactinemia is questionable, and published references are not unambiguous. In the present study, the highest concentrations of i-PTH were found in the control group, what does not confirm observations made by other authors. Such result may suggest absence of catabolic effect of i-PTH on bones of women with hyperprolactinemia. In the group of women with functional hyperprolactinemia, a positive correlation between CAP concentration and lumbar spine, femoral neck, ultradistal radius and total body BMD were shown. CIP correlated positively with ultradistal radius BMD, but CAP/CIP both with Ward's triangle and total body BMD. Effect of PTH differed from effects of its fractions, and some similarity between the groups examined was found in respect to BMD values of the lumbar spine and concentrations of CAP, only. On the other hand, in women with functional hiperprolactinemia the range of effect of PTH and of its fractions was considerable wider and referred to the prevailing part of the skeleton.

CONCLUSIONS

There is no direct benefit of the assessment of parathormone fractions and CAP/CIP ratio in the prognosis of bone metabolism changes in hyperprolactinemia of various origin.

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