Serum concentration of 1–84 (cyclase-activating) and 7–84 (cyclase-inhibiting) parathormone in elderly women with low mineral density of the trabecular bone

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Abstract

Introduction: Ageing may cause an increase in parathormone (PTH) secretion and, subsequently, increased bone resorption and osteoporosis. In recent years two subfractions of PTH have been discovered: cyclase-activating (1–84, CAP) and cyclase-inhibiting (7–84, CIP) PTH. It is not known however, whether these may play a role in the pathogenesis of bone loss in elderly subjects.

Material and methods: Sixty elderly women were examined, of whom 29 had a T-score of the ultradistal radius < –2.5 (median age 75 [70–80] years, BMI 25 [20.6–33.8] kg/m2, creatinine clearance 59.9 [39.2–94.9] ml/min/1.73m2, serum Ca 2.4 [2.2–2.6] mmol/l), while 31 had a T-score > –2.5 (median age 73 [70–86] years, BMI 26.2 [18.8–32.5] kg/m2, creatinine clearance 54.8 [23–119.2] ml/min/1.73m2, serum Ca 2.4 [2.2–2.6] mmol/l). Median bone mineral density (BMD) (DXA, Lunar) of the ultradistal radius was 0.263 (0.195–0.449) g/cm2 and 0.326 (0.236–0.448) g/cm2 (p < 0.0001), with a median T-score of –3.48 and –1.4, respectively. Each patient with a serum concentration of 1–84 and 7–84 PTH was assessed.

Results: Patients with low BMD did not differ from those with higher BMD with regard to serum iPTH (16 [6–51] vs. 11.5 [7–35] pg/ml, p = 0.066) and CIP (6 [1–14] vs. 4.5 [2–13] pg/ml) concentrations. However, serum CAP concentrations (10.5 [4–41] vs. 6 [4–22] pg/ml, p < 0.05) and CAP/CIP ratios (2.0 [0.71–11] vs. 1.25 [0.5–4.2], p < 0.05) were significantly higher in the low BMD group.

Conclusion: In elderly women increased serum CAP concentrations and CAP/CIP ratios are associated with low BMD of the trabecular bone.

Key words: Parathormone, 1–84 PTH, 7–84 PTH, osteoporosis, bone

Streszczenie

Wstęp: Z wiekiem stężenie parathormonu (PTH) może się zwiększać. Konsekwencją tego jest zwiększona resorpcja kości i osteoporozę. W ostatnich latach odkryto dwie frakcje PTH — aktywującą (1–84, CAP) i hamującą (7–84, CIP) cyklazę. Nie jest jasne, czy te frakcje odgrywają rolę w patogenezie utraty masy kostnej u osób starszych.

Materiał i metody: Do badania włączono 60 kobiet. U 29 z nich T-score ultradystalnej części kości promieniowej wynosiło < –2.5 (śr. wieku 75 [70–80] lat, BMI 25 [20,6–33,8] kg/m2, kreatyninna clearance 59,9 [39,2–94,9] ml/min/1,73m2, stężenie Ca w surowicy 2,4 [2,2–2,6] mmol/l), a u 31 kobiet T-score > –2.5 (śr. wieku 73 [70–86] lat, BMI 26,2 [18,8–32,5] kg/m2, kreatyninna clearance 54,8 [23–119,2] ml/min/1,73m2, stężenie Ca w surowicy 2,4 [2,2–2,6] mmol/l). Gęstość mineralna kości (BMD) (DXA, Lunar) ultradystalnej części kości promieniowej wynosiła odpowiednio 0,263 (0,195–0,449) g/cm2 i 0,326 (0,236–0,448) g/cm2 (p < 0,0001), z medianą T-score odpowiednio –3,48 i –1,4. U każdej chorej zauważono 1-84 i 7-84 PTH.

Wyniki: Chore z niskim BMD kości promieniowej nie różniły się od tych z wyższym BMD stężeniem serum iPTH (16 [6–51] vs. 11,5 [7–35] pg/ml, p = 0,066) ani CIP (6 [1–14] vs. 4,5 [2–13] pg/ml) w surowicy. Jednakże stężenie CAP w surowicy (10,5 [4–41] vs. 6 [4–22] pg/ml, p < 0,05) oraz CAP/CIP (2,0 [0.71–11] vs. 1,25 [0.5–4,2], p < 0,05) były znacząco większe u kobiet z niskim BMD.

Wniosk: U starszych kobiet zwiększone stężenie CAP w surowicy i zwiększony iloraz CAP/CIP stowarzyszone są z niską gęstością mineralną kości beleczkowej.

Słowa kluczowe: parathormon, 1–84 PTH, 7–84 PTH, osteoporozę, kości
Introduction

The regulation of bone metabolism is a very complicated process, in which many anabolic and catabolic factors may be involved, including parathormone (PTH), calcitonin and 1,25(OH)₂ vitamin D₃. A predominance of catabolic over anabolic factors leads to increased bone resorption and osteoporosis. There are two main types of primary osteoporosis, postmenopausal and senile. The latter affects subjects older than 65–70 years. A role is played in the pathogenesis of senile osteoporosis by factors such as low peak bone mass, calcium and vitamin D insufficiency and increased PTH secretion [1–4].

PTH acts on the bone in a complex way. It is known that PTH causes an increase in the number and activity of osteoclasts, resulting in bone resorption and loss of calcium from the bone. However, this effect appears to be indirect, as there are no PTH receptors on the osteoclast surfaces, and is mediated by osteoblasts. PTH stimulates the synthesis and secretion of molecules such as IL-6 or RANK-L, which influence osteoclastogenesis [5], and decreases apoptosis of osteoclasts [6]. On the other hand, PTH may, especially during skeleton growth but also when given in pharmacological doses, exert a strong anabolic effect on bone [7, 8]. It seems that this effect is more profound on trabecular bone [9], although the catabolic effect of PTH, for example when hypersecreted by the parathyroid glands in hyperparathyroidism, is shown mainly in cortical bone [10]. These two different actions may depend on the total amount of PTH secreted as well as on changes in pulsatile PTH secretion [11–13]. Nevertheless, it appears that in investigating the influence that physiologically secreted PTH exerts on the bones, bone mineral density (BMD) of the trabecular rather than of the cortical bone should be measured. The ultradistal radius is a measurement site where the bone is composed of the highest percentage of trabecular bone and the lowest percentage of cortical bone.

In the last decade it has been discovered that assessed “intact” PTH in fact includes two subfractions: PTH 1–84 and PTH 7–84 [14–16]. The latter molecule acts in the opposite manner to the former in that it does not activate adenylate cyclase and does not increase serum calcium concentration [17]. It is not clear, however, whether these findings, obtained mainly in vitro, adequately reflect processes taking place in human physiology and pathology. Most of the clinical data published about the PTH subfractions, namely CAP (cyclase-activating peptide) and CIP (cyclase-inhibiting peptide), are based on patients with chronic kidney disease. The original research showed that the intensity of bone turnover in these patients may be dependent on the CAP/CIP ratio [18], but this was not confirmed [19]. Assessment of 1–84 and 7–84 PTH in renal osteodystrophy is probably not necessary for every patient but may be of importance in some cases [20, 21]. It probably offers no advantage over “whole” PTH assessment in patients with primary hyperparathyroidism [22]. No data has been published regarding the role of CAP and CIP in the pathogenesis of osteoporosis. The present study aimed to assess serum concentrations of CAP and CIP in elderly women with low trabecular BMD.

Material and methods

Sixty women aged more than 70 years were included in the study. The protocol was approved by the Bioethical Commission of the Medical University of Silesia, and all the participants signed a form giving their informed consent.

The criteria for exclusion were as follows: a BMI lower than 18 or higher than 35 kg/m², secondary osteoporosis (especially primary or secondary hyperparathyroidism with PTH > 65 ng/ml), previous antifracture treatment, any neoplasm, hyper- or hypocalcaemia, chronic kidney disease with a serum creatinine concentration of more than 250 µmol/l, chronic hepatic disease indicated by AST and AspAT activity elevated more than threefold, and any other condition which was considered to be a contra-indication for the study in the opinion of the investigator. Cigarette smokers were also excluded.

The patients were divided into two groups. The first group comprised 29 women with an ultradistal radius T-score of < –2.5, while the second consisted of 31 women with T-scores ≥ –2.5.

The two groups did not differ with regard to age or basic anthropometric and biochemical parameters (Table I). BMD measurements from other parts of the skeleton differed significantly between the groups (Table II).

Blood samples were taken from each patient for the estimation of serum Ca, P, Na, K, creatinine and PTH subfraction concentrations. Daily excretion of Na, K, Ca, P and creatinine in the urine was also evaluated. All patients were advised to stop calcium and vitamin D treatment one week before urine collection. Creatinine clearance was calculated using the Cockroft-Gault formula [23].

The Duo PTH IRMA kit (Scantibodies Laboratory Inc., USA) was used to assess PTH subfraction concentrations. This kit allows for “whole” PTH (1–84 PTH = CAP) and “total” PTH (comprises 1–84 and 7–84 fragments) evaluation [24]. All remaining blood and urine parameters were assessed by routine laboratory methods. Bone densitometry (the dual-energy X-ray method, DXA) was performed using a LUNAR machine. The BMD (g/cm²) of the radius, femoral neck and lumbar spine were measured and the T-score calculated. Cortical bone was assessed in the proximal one third of...
the radius shaft (33%) and trabecular bone in the ultradistal part of the radius.

Statistical analysis was performed using STATISTICA software. The Mann-Whitney test was used for comparison between the two groups, with the Spearman rank test being used for univariate correlations. The influence on dependent variables was verified by stepwise backward regression multivariate analysis.
Results

The basal data of both groups are shown in Tables I and II. As can be seen the patients in the two groups did not differ with regard to anthropometric and biochemical parameters. In patients with a low BMD of the ultradistal part of the radius a significantly lower BMD was noted than at other measurement sites.

There was no significant difference between the groups with regard to serum "total" PTH (p = 0.066) and CIP concentrations, but serum CAP concentrations and CAP/CIP ratios were significantly higher in patients with low BMD of the ultradistal radius (Fig. 1). However, if the patients were divided into subgroups according to BMD of the spine or proximal radius, no significant differences were found (data not shown). If a femoral neck T-score of –2.5 was used as a division criterion, the subgroups with and without osteoporosis differed significantly with regard to femoral neck, spine and proximal radius measurements. It should be mentioned, however, that the interpretation of results was difficult.

Because of the relatively small number of patients the whole group of 60 subjects was included in the multivariate analysis. Only those variables that showed a significant relationship in the univariate analysis were assessed. In the multivariate analysis "total" PTH, CAP and CIP respectively, showed an independent relationship only with serum phosphate concentration (β = –0.34, p = 0.041, β = –0.39, p = 0.0019 and β = –0.26, p = 0.046, respectively). In the univariate analysis significant negative correlations of ultradistal radius and femoral neck BMD and T-score with serum PTH and CAP concentrations were found (not shown). However, despite this, in the multivariate analysis femoral neck BMD and T-scores correlated independently only with the body mass (β = 0.463, p=0.00019 and β = 0.472, p = 0.00014, respectively). No independent correlation was shown between the ultradistal radius BMD and any of the parameters examined.

Discussion

The two groups examined were comparable with regard to age and anthropometric (Table I) and biochemical parameters (Table II).

It is not surprising that the two groups, divided according to their ultradistal radius T-scores, differ significantly with regard to femoral neck, spine and proximal radius measurements. It should be mentioned, ho-
however, that for some of the patients the T-scores were different in different sites. This situation is well documented [25], although it may cause some problems with data interpretation. For this reason it was impossible to stratify and compare the group under examination with regard to BMD measurements for different sites. The subjects were matched appropriately according to age and weight if the ultradistal radius was used as a stratification criterion, but they differed significantly with regard to these parameters when BMD measurements from other sites were used for this purpose.

The aim of the study was to assess the influence of PTH subfractions on trabecular bone. It is known that PTH acts physiologically not only on cortical bone, but also, and even predominantly, on trabecular bone [9, 26]. Conversely, pathologically increased PTH secretion (as in primary or secondary hyperparathyroidism) mainly influences cortical bone [27]. In spite of the fact that PTH may play a role in the pathogenesis of senile osteoporosis, PTH concentrations in these patients are not above the normal range. In the population examined the median PTH values were rather low in both groups (Fig. 1), although they were slightly higher in patients with low BMD. It is possible that in these patients changed pulsatile secretion patterns may be of importance, although the data regarding pulsatile PTH secretion in osteoporosis patients are scarce (in patients with secondary hyperparathyroidism the amplitude and frequency of pulses increases as well as the basal secretion [13]). Samuels et al. [28] showed that there is no difference in the pulsatile patterns of PTH secretion of young and postmenopausal women. Conversely, it has been shown in a small population of patients that pulsatile PTH secretion in postmenopausal osteoporosis is decreased [29]. It is also known that pulsatile pharmacological administration of 1-34 PTH causes a distinct increase in trabecular bone (spine) BMD [8]. In our study it was impossible for various reasons to investigate this issue, and attention was paid to another pathogenetic aspect of senile osteoporosis.

As far as we know, this is the first paper to assess the concentration of PTH subfractions, the 1–84 and 7–84 peptides, specifically in subjects with decreased BMD of the trabecular bone and in patients with osteoporosis. As shown in Figure 1, the serum CAP concentration and CAP/CIP ratio are significantly higher in subjects with an ultradistal radius T-score lower than –2.5. The difference in serum “total” PTH concentrations between the two groups examined was of borderline significance. Such results are not surprising, as the cyclase-activating subfraction of PTH (CAP) causes an increase in bone resorption, it could be responsible for the decreased BMD in such patients. In univariate analysis significant negative correlations were found between serum CAP concentrations as well as the CAP/CIP ratio and the T-score of the ultradistal radius. Correlations of borderline significance between CAP level and the CAP/CIP ratio and ultradistal radius BMD were also found (data not shown). It should be mentioned, however, that the univariate correlations were not strong and in the multivariate analysis these results were not confirmed. As the number of patients was relatively small, the multivariate analysis was performed on the total group and not on the separate subgroups. Consequently, this may have influenced the results. Additionally, BMD is influenced by many genetic and environmental factors and only some of these (e.g. body weight, the only factor independently correlating with femoral neck BMD) were included in the analysis. The absence of many of these factors may of course be misleading.

The CAP/CIP ratio in the group examined was definitely higher than 1.0. In patients with chronic kidney disease the mean CAP/CIP ratio is close to 1.0. In approximately half the ratio is lower and in the other half it is higher, sometimes much higher [18]. Gao et al. [14] have shown that in healthy subjects aged 18–62 years its value is 1.7, which is similar to the mean value for the whole group examined in this study, but lower than the CAP/CIP ratio in the subgroup of patients with a low ultradistal radius BMD. Comparison with such a “historical control” is, of course, not really justified, but the results seem reasonable. The lower BMD in subjects with a higher CAP/CIP ratio may be caused by increased bone resorption. There are no published data, however, regarding the influence of the CAP/CIP ratio or PTH subfractions on BMD or bone turnover in healthy subjects.

Of course, this study does not allow us to draw any conclusions about a causal relationship between serum CAP concentration or CAP/CIP ratio and low trabecular bone mass. It is only possible to state the presence of an association between these parameters.

Conclusions

In conclusion, in elderly women, low bone mineral density of the ultradistal radius is associated with a higher concentration of the cyclase-activating subfraction of PTH (CAP) and a higher CAP/CIP ratio. However, further research is needed before the question of whether this is a causal relationship can be answered.

References


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