Virchows Archiv (1995) 426:127–134

ORIGINAL ARTICLE

Martin Vogel · Michael Hahn · Günter Delling

Trabecular bone structure in patients with primary hyperparathyroidism

Received: 24 February 1994 / Accepted: 11 October 1994

Abstract To evaluate the effects of increased parathyroid hormone (PTH)-secretion on trabecular bone structure in patients with primary hyperparathyroidism (PHPT) we have analysed iliac crest biopsies from 84 patients (38 male, 46 female, age 20–85 years) with surgically proven PHPT by using quantitative histomorphometry. As there might be an influence of age or sex, subjects were divided into 4 subgroups according to age (younger than 50 years, older than 50 years) and sex. Eighty four age and sex matched autopsy cases of accidental death served as controls. When compared with age matched controls, trabecular bone volume (BV/TV) and trabecular diameter in PHPT were increased. Trabecular density in PHPT was elevated significantly in the older age-groups. These results suggest a preservation of intertrabecular connectivity, which we were able to confirm by measurement of the number of intertrabecular nodes and trabecular bone pattern factor (TBPf). No differences were demonstrated between male and female subjects. Furthermore, no variations according to the histological type (with or without endosteal fibrosis) could be demonstrated in our material. We conclude that increased trabecular bone volume in PHPT is the result not only of thicker trabecula but also of a reduction of the age-dependent loss of complete trabecular plates due to perforations. Thus PHPT leads to a substantial preservation of intertrabecular connectivity.

Key words Trabecular bone structure · Primary hyperparathyroidism · Bone histomorphometry

Introduction

The alterations of bone structure in patients with primary hyperparathyroidism (PHPT) were first described by Recklinghausen in 1891 [35]. Since this time so-called brown tumours have been considered to be a typical feature of PHPT but previous study of iliac crest biopsies in 391 cases of surgically proven PHPT [10] has shown that there are four distinct types of finding. Severe fibroosteoclasia leading on to the development of brown tumours (type IV) was present in only 4% of all cases. However, as many as 49% showed a specific, but very often mild, endosteal fibrosis (type III). In 46% there was a stimulation of endosteal remodelling surfaces without endosteal fibrosis (type II) and in a very small number of cases no differences from normal bone tissue could be observed (type I).

With the possibility of using parathyroid hormone (PTH) pharmacologically, the resulting effects of chronically elevated PTH levels on trabecular bone have opened up areas of increasing interest. Parfitt (1976) [23] has reported that application of PTH in animals can cause both osteosclerosis and osteopoenia depending on the dose and duration of treatment; the age of the animals undergoing treatment is also of great importance.

In man, several studies applying PTH fragments alone or in combination with other drugs have demonstrated a net positive effect on trabecular bone volume in idiopathic osteoporosis [22, 27, 31, 32, 33, 36, 39]. These studies have never exceeded two years in duration and were carried out on a few patients. Data on the long term application of PTH are not available.

Former histomorphometric studies in iliac crest biopsies of patients with PHPT have failed to show changes in trabecular bone volume (BV/TV) [6, 7, 12], whereas others have demonstrated an increase of BV/TV [21, 25, 26, 40]. It has been a matter of speculation whether differences in PTH action in males or females at different ages exist [15, 34], but this has never been investigated systematically.

The aim of the following study was to analyse trabecular bone structure in a large number of patients with PHPT to determine whether different patterns of reaction may exist according to age and sex. Furthermore, it is conceivable that bone volume and trabecular bone struc-

M. Vogel (✉) · M. Hahn · G. Delling
Department of Bone Pathology, Institute of Pathology, University of Hamburg, Martinistrasse 52, D-20246 Hamburg, Germany

ture might depend on the histological type of PHPT, as mentioned by Lloyd [19].

Patients and methods

Iliac crest bone biopsies of 84 patients (38 male and 46 female) with surgically proven PHPT were examined. These biopsies were derived from a collection of 391 patients with PHPT(Delling et al., 1987). All biopsies included fulfilled the following criteria: a sufficient amount of trabecular bone for quantitative histomorphometry (measuring field more than 30 mm^2), normal renal function (Serum-creatinine<1.0 mg/ml) and no brown tumours. Biopsies were taken at parathyroidectomy. The patients' age ranged from 20 to 85 years (mean=50.5 years). PHPT was detected in 16 cases through nephrolithiasis, whereas all other patients were detected by routine examination of calcium and/or PTH levels for other reasons. Mean serum calcium levels in our cases were 3.1 mmol/l±0.5 mmol/l (normal: 2.1–2.7 mmol/l). Serum alkaline phosphatase levels in PHPT were 184 U/l±75 U/l (normal: 55–170 U/l). Serum-phosphorus in patients was in the lower normal range. PTH-levels were increased in all patients but these data were derived by different methods and are not comparable. Serum levels of alkaline phosphatase, calcium and phosphate were recorded from the first day of admission to the hospital.

Eighty four autopsy cases (38 male and 46 female) were used as healthy controls. Their age ranged from 19 to 87 years (mean=50.1 years). In all of them death was sudden, due to accidents. None had any history of severe diesease or prolonged bedrest in the past. Skeletal disorders were excluded histologically.

To allow for the differentiation of age or sex-related influences on bone changes all subjects were divided into 4 groups according to sex and age (≤50 years/>50 years). In women, this subclassification allows an approximate differentiation between the pre- and postmenopausal state and enables comparison with data from other authors [24]. The number and age of patients in these groups are shown in Table 1.

Iliac crest biopsies were taken in a vertical direction 2 cm below the anterior superior iliac spine according to the procedure described by Burkhardt, 1966 [4]. Subsequently they were embedded undecalcified. Sections 5 µm thick were stained using Goldner, von Kossa modification, and toluidine blue reaction [10, 14].

All morphometric measurements were done in the spongy bone of the iliac crest. This was defined as an area at least 2 mm distant from the endosteal site of cortical bone. The field for morphological evaluation was at least 30 mm^2 in each case. One single section of each biopsy was examined.

The following parameters were measured directly:

1. BV/TV (%), trabecular bone volume: by means of a point counting system (Merz-grid). All points covering mineralized bone and osteoid were divided by the number of points covering the tissue area (T.Ar).
2. Trabecular diameter (µm): by means of a semi-automatic image analysing system (IBAS I, Kontron, FRG). Each time a randomly oriented test line covers a trabeculum, the shortest distance from one surface to the other is measured. The median value of at least 200 measurements for each biopsy is defined to be the trabecular diameter. To get the trabecular diameter for each individual case we choose the median value instead of mean value because the frequency distribution of all single measurements is not normally distributed. Trabecular plates which are oriented parallel to the cutting surface of the histological section tend to result in very high values for trabecular diameter.
3. Trabecular density (n/mm): the number of trabecula covered by a randomly oriented test line divided by the length of the test line. The mean value of at least 200 measurements is chosen.
4. W.Th. (µm) wall thickness according to the method of Kragstrup [18].
5. Number of intertrabecular nodes (=node count/mm^2) as described by Compston et al. [8]. By means of an IBAS II image analyser the binary image was skeletonised and nodes were defined as single pixels with at least three pixels in its 3×3 pixel neighborhood.
6. TBPf (mm-1), trabecular bone pattern factor, as described in detail by Hahn et al. [14]. This involves using an automatic image analysing system (IBAS II, Kontron, FRG) to obtain a binary image of trabecular bone (stained using the van Kossa reaction). Bone area (B.Ar;=A1) and bone perimeter (B.Pm; =P1) are then measured. After an artificial dilatation of trabecula for about 5 µm, bone area (B.Ar; =A2) and bone perimeter (B.Pm; =P2) are measured again. TBPf is calculated on the basis of the following formula: TBPf=(P1–P2)/(A1–A2). The basic idea of this procedure is that well-connected structures show a lot of concave surfaces and isolated structures show a lot of convex surfaces. Dilatation of a convex surface leads to an increase in perimeter, whereas dilatation of a concave surface leads to a decrease in perimeter. High values of TBPf indicate a lot of convex surfaces (poorly connected structures), whereas low values indicate a lot of concave surfaces (well-connected structures).

Measurements of bone area (B.Ar), tissue area (T.Ar) and bone perimeter (B.Pm) were carried out using a 63-fold magnification and a point counting procedure [9, 38]. Osteoblast surface and Howships lacunae were measured at a 160-fold magnification. The percentage of lines of the Merz-grid covering osteoblasts (Howships lacunae) and all lines covering bone surface gives the value for Ob.S/BS (%) and ES/BS (%).

Distances were measured at a 63-fold magnification by means of a semi-automatic computer assisted image analysing system (IBAS I, Kontron, FRG). Test line measurements were obtained in each case for at least 30 different fields (leading to at least 200 counts per parameter and section). Orientation of the test line was determined from a random table.

The differentiation in four distinct histological types of pHPT was done according to Delling [10]. Type I represents normal bone tissue; type II is a stimulation of endosteal remodelling without fibrosis; type III shows endosteal fibrosis and type IV are all biopsies with the presence of brown tumours.

If not indicated otherwise all values are given as mean values±standard deviation (SD). For calculation of significant difference student's *t*-test was used in all cases (*=$P<0.05$; **=$P<0.01$; ***=$P<0.001$).

Table 1 Age and number of cases in each group

		≤50 years Age±SD (years)	>50 years Age±SD (years)
Male	PHPT	35.4±12.3 (n=21)	63.8±9.0 (n=17)
	Control	33.4±12.6 (n=21)	65.1±11.5 (n=17)
Female	PHPT	38.4±10.1 (n=22)	63.6±7.9 (n=24)
	Control	37.0±9.9 (n=22)	64.0±8.0 (n=24)

Results

All cases with PHPT (type II and III) studied showed an intact trabecular bone structure (Fig. 1). Nearly all cases with PHPT had increased endosteal remodeling, which was revealed by a high number of osteoclasts and osteoblasts. Of all cases 54% had mild endosteal fibrosis only.

Bone volume (BV/TV)

In normal subjects ≤50 years BV/TV was 20.8%±4.7% (male) and 21.0%±3.7% (female) respectively, whereas BV/TV in cases >50 years was 14.4%±5.6% (male) and 14.9%±4.8% (female) respectively.

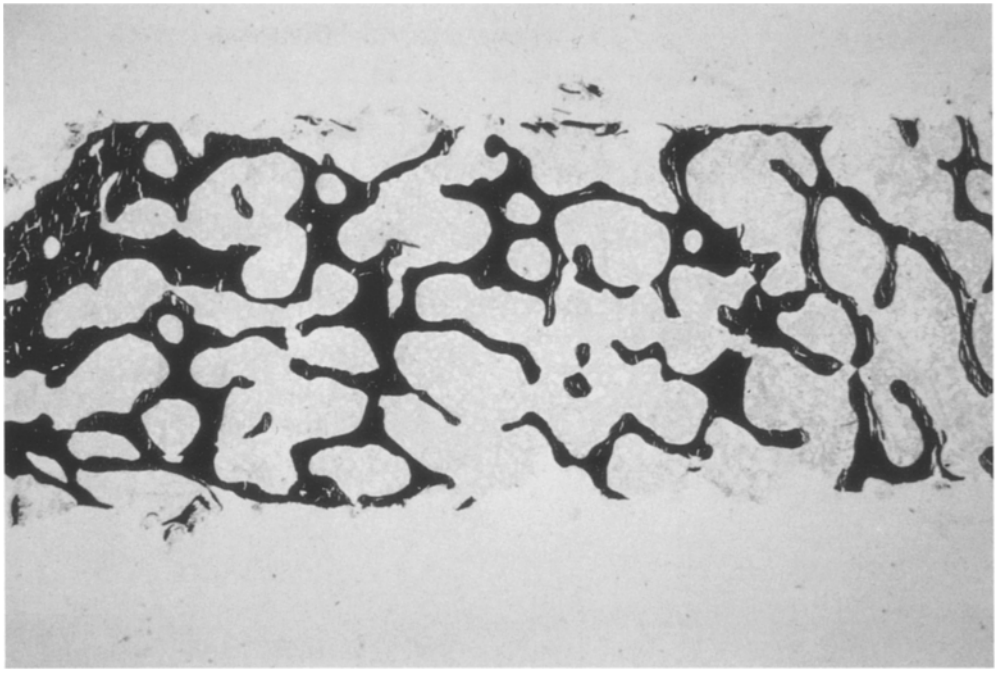

Fig. 1 Histological section, primary hyperparathyroidism (PHPT). Iliac crest bone biopsy of a 51-year-old woman with surgically proven PHPT. Trabecula are wide and well-connected. No woven bone or destructive perforations are present. (von Kossa stain, 10×)

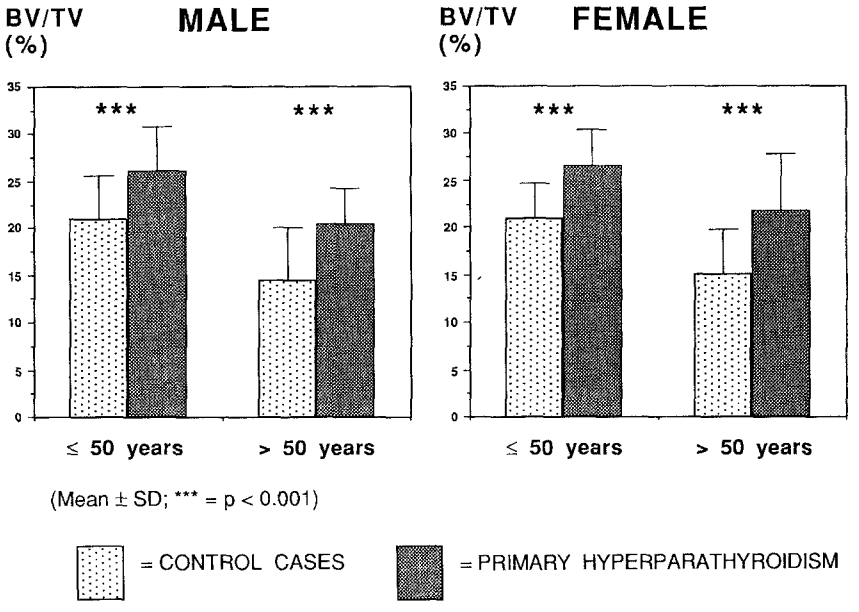

Fig. 2 Trabecular bone volume (BV/TV). Males and females were each divided into sub-groups ≤50 years and >50 years. In all groups and both sexes BV/TV is relatively higher in PHPT compared to the corresponding control groups

In PHPT bone volume was significantly increased in all corresponding groups ($P<0.001$). BV/TV in groups ≤50 years was 26.05%±4.8% (male) and 26.5%±3.8% (female). In cases >50 years it was 20.4%±3.9% (male) and 21.7%±6.1% (female) (Fig. 2).

When we performed a correlation between BV/TV and the number of Howship'lacunae (ES/BS) we got an coefficient of correlation of $r=0.05$. The correlation between BV/TV and Osteoblastic Surface (Ob.S/BS) was $r=0.13$.

Trabecular diameter

Male and female control subjects showed no significant decrease of trabecular diameter between the younger (≤50 years) and the older (>50 years) groups ($P>0.05$).

Compared with corresponding groups of normal subjects in PHPT we found an increase in trabecular diameter by between 16.8 µm and 27.0 µm. An influence of age or sex on this widening of trabecula could not be shown (Fig. 3).

Trabecular density

In normal subjects, loss of complete trabecula mainly contributed to age-dependent bone loss. In subjects ≤50 years there were no statistically significant differences between PHPT and age-matched controls.

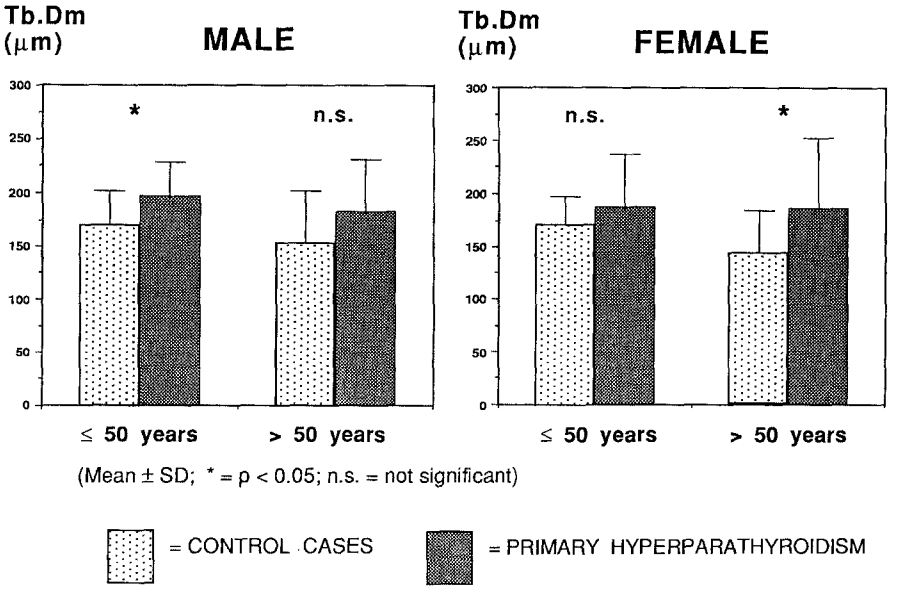

Fig. 3 Trabecular diameter (Tb.Dm). In PHPT in both age groups and both sexes trabecular diameter is higher compared to normal subjects

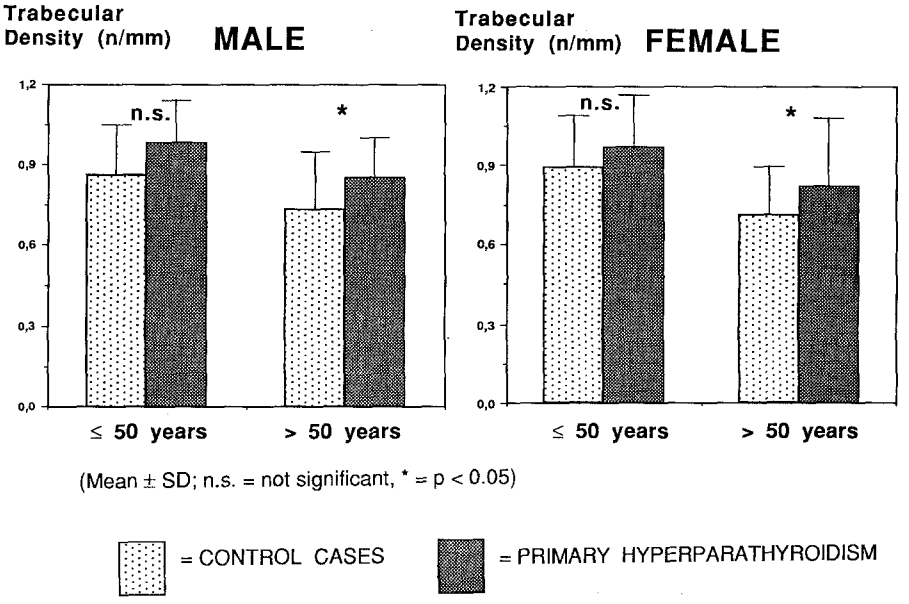

Fig. 4 Trabecular density. Trabecular density is increased in PHPT. Compared to controls there is a relative increase of trabecular density in PHPT: this is more pronounced in older subjects

In older subjects there were significantly higher values of trabecular density in male and female subjects with PHPT when compared with their corresponding control cases. Relative increases were 13.9% (male≤50 years), 9.0% (female≤50 years), 16.4% (male>50 years) and 15.5% (female >50 years) respectively (Fig. 4).

Mean wall thickness (W.Th)

Wall thickness is a variable which defines the amount of newly formed bone by osteoblasts. In control subjects W.Th decreased moderately during the course of aging. Compared to corresponding groups W.Th was increased in PHPT (Fig. 5). This points to an increased osteoblastic activity on tissue level. Mean values for PHPT (control) were: males≤50 years 44.4±5.7 μm (42.5±3.8 μm); males >50 years 45.7±5.5 μm (41.5±4.8 μm); females ≤50 years 45.2±5.0 μm (42.5±3.1 μm); females >50 years 43.7±6.2 μm (39.3±3.4 μm).

Number of intertrabecular nodes (mm^{-2})

In control subjects there was a moderate age-dependent decrease in the number of intertrabecular nodes (count/mm-2 in) males ($P<0.05$) and a pronounced change in females ($P<0.001$). In PHPT there was a significantly higher value of node count/mm^2 between all corresponding age groups. The values for each group are given in Fig. 6.

Trabecular bone pattern factor (TBPf)

High values of TBPf indicate a poor rate of connectivity of trabecula. As already described by Hahn et al. [14], in

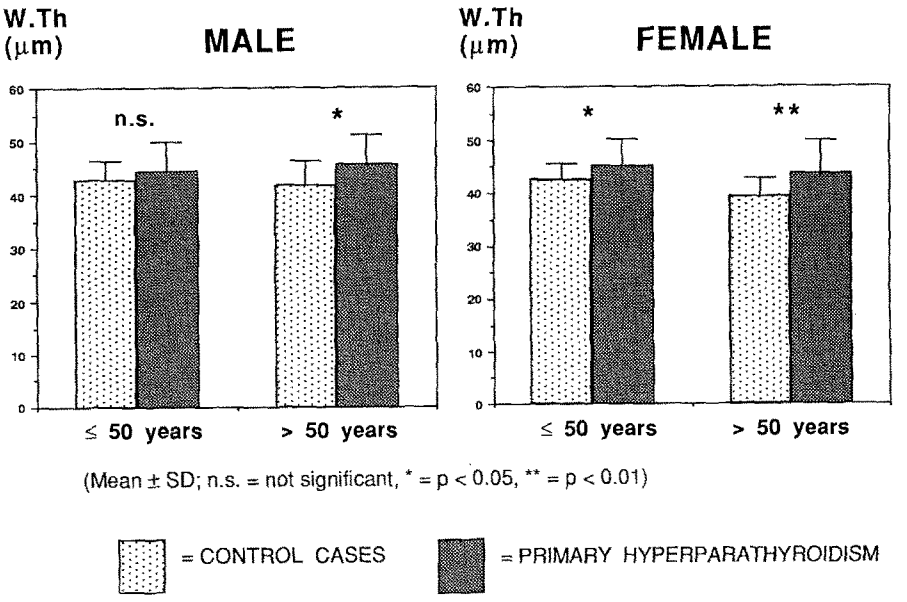

Fig. 5 Wall thicknes (W.Th.). W.Th is the mean thickness of newly formed bone packages by osteoblasts. Its relative increase in relation to corresponding control subjects is 2.5% (males≤50 years), 36.6% (males>50 years), 15.1% (females ≤50 years) and 19.1% (females >50 years)

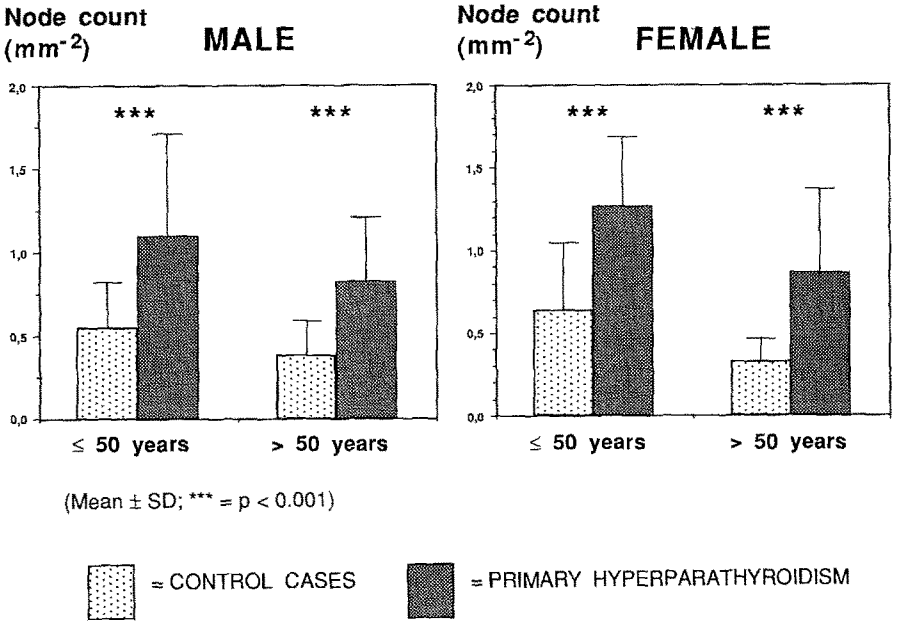

Fig. 6 Intertrabecular nodes (node count/mm^2). The node count/mm^2 gives significant differences between pHPT and controls in all age groups and in both male and female subjects.

another cohort of control subjects there was an age dependent increase of TBPf in females ($P<0.05$), whereas in males no age-related change of TBPf could be determined. Furthermore, in PHPT, TBPf was decreased in all groups (Fig. 7). This points towards a much better rate of connectivity in terms of a decreased number of isolated trabecula in the two-dimensional bone sections.

Histological type (with or without endosteal fibrosis)

All patients were considered to be one group and divided according to the presence of endosteal fibrosis (type III, n=49) or not (type II, n=33, type I, n=2). Values for each type were:
BV/TV: 24.6±6.3% (type II); 23.1±6.4% (type III)
Calcium: 12.3±1.5 mg% (type II); 12.9±2.0 mg% (type III)
Alkaline phosphatase: 103.7±60.2 U/l (type II); 241.5 ±182.5 U/l (type III)
Percentage of trabecular surface covered with Howship'lacunae (ES/BS): 4.25±2.15% (type II); 6.05±3.56% (type III)
Percentage of trabecular surface covered by osteoblasts (Ob.S/BS): 3.31±2.26% (type II); 4.58±3.18% (type III).

Discussion

Our study revealed higher values of trabecular bone volume (BV/TV) in the iliac crest of patients with primary hyperparathyroidism (PHPT) when compared with age-

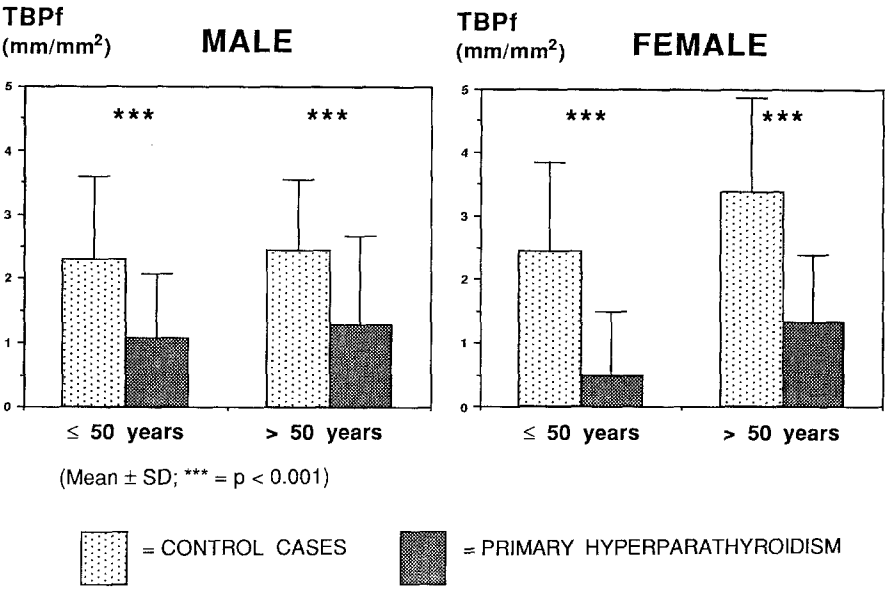

Fig. 7 Trabecular bone pattern factor (TBPf). TBPf is an index of the relationship between concave and convex surfaces. A lot of concave surfaces (i.e. low values of TBPf) indicate a well-connected bone pattern. A lot of convex surfaces are indicative of many isolated trabecula and many perforations. In PHPT there is a substantial improvement in the rate of intertrabecular connectivity in all groups

matched autopsy cases after accidental death. At first this would seem to contradict the traditionally accepted view that patients with PHPT have a decreased amount of bone tissue, as can be demonstrated by means of different non-invasive methods for measurement of bone density [3, 20, 28, 30]. Nevertheless, it seems that at different sites (distal or proximal radius, or lumbar spine) there are quite different responses of bone to chronically elevated levels of PTH [20, 28]. Furthermore, Pfeilschifter et al. [28], demonstrated that mild HPT results in increased bone density of trabecular bone in the lumbar spine whereas symptomatic HPT results in decreased bone density.

Our findings of increased trabecular bone volume (BV/TV) in PHPT are not unique. Genant et al. [13] and Chan et al. [5] both described cases of osteoscleroses in primary and secondary hyperparathyroidism. Obviously, the effects of parathyroid hormone (PTH) on bone are dependent on the duration, extent and pattern of PTH secretion [16]. Piraino et al. [29] have demonstrated increased bone volume in patients with renal osteodystrophy, where such findings confirmed a dependence on the histological type and the serum level of PTH. Furthermore, in some clinical studies it has been demonstrated that cyclical or pulsatile doses of PTH fragments can cause net gains in bone volume [22, 31, 32, 33, 36, 39].

Histomorphometrical analyses carried out by some groups [6, 7, 12] have not been able to demonstrate changes in bone volume in PHPT, whereas in others [21, 25, 26, 40] increased levels of BV/TV in PHPT have been established. The interpretation of these different results is quite difficult. Unfortunately, we do not know anything about the histological type of PHPT in these studies. As suggested by Lloyd, [19] and shown by Piraino et al. [29] (in patients with renal osteodystrophy) in hyperparathyroidism the alterations in bone volume may depend on the histological type seen in bone biopsies. In our study most patients were detected during routine examinations of calcium levels and some were noticed on the basis of recurrent nephrolithiasis. Mild endosteal fibrosis was present in 54% of cases. Cases with brown tumours or woven bone were not present. Indeed, patients with endosteal fibrosis had higher levels of serum calcium levels and serum alkaline phosphatase activity when compared with patients without endosteal fibrosis. But, nevertheless, in our study biopsies both with and without endosteal fibrosis showed no different bone microarchitecture.

From the pathophysiology of bone remodelling a relative gain in trabecular bone volume (BV/TV) can be achieved in two ways; firstly by a widening of individual trabecula and secondly by an increase in the number of trabecula. This distinction is a particularly important one since in terms of bone strength an increased number of trabecula is clearly superior [17]. In PHPT in both sexes and all ages we find a widening of trabecular diameter by between 16.8 µm and 29.6 µm. This widening is in accordance with studies from Parisien et al., [25, 26]. It seems to be due to a stimulation of osteoblastic bone formation on tissue level, as can be shown by increased wall thickness (W.Th.). Such findings are corroborated in another study with tetracycline marked cases where an increased mineral apposition rate in PHPT was demonstrated [40] and an increased lifespan of osteoblasts [6] may contribute to the effect described here.

The widening of trabecula in our material can explain an increase of BV/TV by between 9.8% and 29.2% only. Measurement of BV/TV showed values which were higher by 25.2% to 45.6% when compared with age matched controls.

The trabecular density increased by between 9.0% and 16.4%. How is it possible to obtain an increase in trabecular density in PHPT? As the genesis de novo of absolutely new trabecula is not compatible with current ideas of bone turnover it is most likely that an increased number of trabecula is the result of a reduced frequency

of trabecular plate perforations. As shown by Parfitt et al. [24], the age-dependent loss of bone is mainly the result of a loss of whole trabecula, due to their perforation by osteoclastic bone resorption. There exist a wide variety of agents stimulating motility of osteoclasts [1, 2, 41] and if PTH stimulates in vivo osteoclastic motility, then an unchanged resorption activity of each osteoclast should lead to a decreased depth of resorption lacunae. Indeed, in a histomorphological study decreased depth of resorption lacunae in PHPT was found [12]. Furthermore, an unchanged resorptive activity of osteoclasts in moderate PHPT has been demonstrated by means of electron microscopy [11]. Because of an increased trabecular diameter in PHPT, the probability of perforations can be reduced drastically even when there is an unchanged depth of the lacunae. Our data revealing cases with an increased trabecular density suggest a better rate of intertrabecular connectivity. This is supported by the direct measurement of intertrabecular nodes (node count /mm^2), which were increased in all groups with PHPT. Each perforation leads to a loss of connectivity in the two-dimensional section but only a perforation which is located at a node would result in a reduction of node count/mm^2. Therefore, we would expect no real dependency between the node count/mm^2 and the number of perforations.

TBPf (Trabecular bone pattern factor) is a parameter for the relationship between convex and concave surfaces [14]. Therefore, TBPf gives an value for the number of isolated trabecula. The age-dependent transformation of trabecular plates into rods following perforation leads to an increase of convex surfaces in two-dimensional sections. These can be quantified by TBPf. As a result, in our data TBPf was decreased in all groups with PHPT indicating a reduced number of perforations in PHPT.

The increased rate of intertrabecular connectivity and a reduced perforation rate in our cases with PHPT suggest greater stability of trabecular bone. This is underlined by other data [21] demonstrating increased compression strength of the cancellous part of vertebrae in PHPT. In patients with renal osteodystrophy and secondary hyperparathyroidism the incidence of fractures is reduced when compared with normal cases [29]. Moreover, Saphier et al. [37] have found a decreased fracture rate in patients with osteoporosis with increased levels of PTH compared with patients without increased levels of PTH.

Our data demonstrate the ability of PTH to induce anabolic effects in trabecular bone of the iliac crest in patients with PHPT. A stimulation of bone cell proliferation and endosteal fibrosis did not lead to statistically significant differences in this effect. Furthermore, the sex of the individuals with PTH was of no importance to the changes in the trabecular response to this disease.

Whether the application of PTH leads to an improved trabecular bone structure comparable to the one seen in PHPT is a question which can not be answered on the basis of our data. Clinical studies dealing with the therapy of osteoporosis by means of pulsatile hPTH (1-38) have provided quite good results [27, 36], but such findings need to be confirmed by case studies covering a larger number of patients.

References

1. Alam AS, Moonga BS, Bevis PJ, Huang CL, Zaidi M (1993) Amylin inhibits bone resorption by a direct effect on the motility of rat osteoclasts. Exp Physiol 78:183–196
2. Azria M, Behhar C, Cooper S (1993) Lack of effect of ipriflavone on osteoclast motility and bone resorption in in vitro and ex vivo studies. Calcif Tissue Int 52:16–20
3. Bergenfelz A, Lindergard B, Ahren B (1992) Biochemical variables associated with bone density in patients with primary hyperparathyroidism. Eur J Surg 158:473–476
4. Burkhardt R (1966) Präparative Voraussetzungen zur Klinischen Histologie des menschlichen Knochenmarks. Blut 14:30–45
5. Chan YL, Furlong TJ, Cornish CJ, Posen S (1985) Dialysis osteodystrophy. A study involving 94 patients. Medicine 64: 296–309
6. Charhon SA, Edouard EC, Arlot ME, Meunier PJ (1982) Effects of parathyroid hormone on remodeling of iliac trabecular bone packets in patients with primary hyperparathyroidism. Clin Orthop 162:255–263
7. Christiansen P, Steiniche T, Vesterby A, Mosekilde L, Hessov I, Melsen F (1992) Primary hyperparathyroidism: iliac crest bone volume, structure, remodelling, and balance evaluated by histomorphometric methods. Bone 13:41–49
8. Compston JE, Mellish RW, Garrahan NJ (1987) Age-related changes in iliac crest trabecular microanatomic bone structure in man. Bone 8:289–292
9. Delling G (1975) Endocrine bone diseases. Veröffentlichungen aus der Pathologie. Büngeler W, Eder M, Lennert K, Peters G, Sandritter W, Seifert G (eds) Gustav Fischer Verlag, Stuttgart. 109 pp
10. Delling G (1987) Bone morphology in primary hyperparathyroidism – a qualitative and quantitative study of 391 cases. Appl Pathol 5:147–159
11. Delling G, Ziegler R, Schulz A (1975) Bone cells and structure of cancellous bone in primary hyperparathyroidism. A histomorphometric and electron microscopic study. Calcif Tis Res 21:278–283
12. Eriksen EF, Mosekilde L, Melson F (1986) Trabecular bone remodelling and balance in primary hyperparathyroidism. Bone 7:213–221
13. Genant HK, Baron JM, Paloyan E, Jowsey J (1975) Osteosclerosis in primary hyperparathyroidism. Am J Med 59:104–113
14. Hahn M, Vogel M, Pompesius Kempa M, Delling G (1992) Trabecular Bone Pattern Factor – A New Parameter for Simple Quantification of Bone Microarchitecture. Bone 13:327–330
15. Heaney RP (1975) Skeletal remodeling physiology and its relation to metabolic bone disease. NY State J Med 75: 1656–1661
16. Hesch RD, Busch U, Prokop M, Delling G, Rittinghaus EF (1989) Increase of vertebral density by combination therapy with pulsatile 1–38 hPTH and sequential addition of calcitonin nasal spray in arteoporotic patients. Calcif Tis Int 44:176–180
17. Kleerekoper M, Goldstein SA, Feldkamp LA, Flynn MJ, Dickie D, Parfitt AM (1987) Cancellous bone architecture and bone strength. In: Osteoporosis 1987. C. Christiansen, J.S. Johansen, B.J. Riis (eds). Osteopress ApS. Copenhagen, Denmark, pp. 294–300
18. Kragstrup J (1985) Osteons in trabecular bone. Laegeforeningens Forlag, Copenhagen, Denmark, pp 1–15
19. Lloyd HM (1968) Primary hyperparathyroidism: analysis of the role of the parathyroid tumor. Medicine 47:53–71, 1968
20. Minisola S, Rosso R, Romagnoli E, Pacitti MT, Scarnecchia L, Carnevale V, Mazzuoli G (1993) Trabecular bone mineral density in primary hyperparathyroidism: relationship to clinical presentation and biomarkers of skeletal turnover

21. Mosekilde L, Mosekilde M (1988) Iliac crest trabecular bone compressive strength and ash weight is increased in moderate primary hyperparathyroidism (abstract). In: Proceedings of the 5th International Congress on Bone Morphometry. H. Takahashi (ed). Niigata, Japan, 1988, A 111
22. Neer RM, Slovik D, Doppelt S, Daly M, Rosenthal D, Lo C, Potts J (1987) In: Osteoporosis 1987. Christiansen C., Johansen J.S., Riis B.J. (eds). Osteopress ApS, Copenhagen, Denmark, 1987, pp. 829–835
23. Parfitt AM (1976) The actions of parathyroid hormone on bone: relation to bone re-modelling and turnover, calcium homeostasis, and metabolic bone disease. Part III Metabolism 25:1033–1069
24. Parfitt AM, Matthews CHE, Villanueva AR, Kleerekoper M, Frame B, Rao DS (1983) Relationship between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. J Clin Invest 72:1396–1409
25. Parisien M, Silverberg SJ, Shane E, De la Cruz L, Lindsay R, Bilezikian P, Dempster DW (1990) The histomorphometry of bone in primary hyperparathyroidism: preservation of cancellous bone structure. J Clin Endocrinol Metab 70:930–938
26. Parisien M, Mellish RW, Silverberg SJ, Shane E, Lindsay R, Bilezikian JP, Dempster DW (1992) Maintenance of cancellous bone connectivity in primary hyperparathyroidism: trabecular strut analysis. J Bone Miner Res 7:913–919
27. Parsons JA, Bernat M, Bijvoet OL, Meunier PJ, Neer RM, Potts J, Reeve J, Renier JC, Vismans J (1979) Low doses of synthetic fragment of human parathyroid hormone (hPTH 1-34) as a stimulus to bone formation. In: Osteoporosis II, U.S. Barzel (ed), Grune and Stratton, New York, pp. 151–159
28. Pfeilschifter J, Siegrist E, Wuster C, Blind E, Ziegler R (1992) Serum levels of intact parathyroid hormone and alkaline phosphatase correlate with cortical and trabecular bone loss in primary hyperparathyroidism. Acta Endocrinol Copenh 127: 319–323
29. Piraino B, Chen T, Cooperstein L, Serge G, Puschett J (1988) Fractures and vertebral bone mineral density in patients with renal osteodystrophy. Clin Nephrol 30:57–62
30. Pozzi-Mucelli RS, Kanton A, Genant HK, Cann CE, Ettinger B, Kolb FO (1983) Quantitative bone mineral analysis in primary hyperparathyroidism (abstract). J Comput Assist Tomogr 7:555
31. Reeve J, Meunier PJ, Parsons JA, Bernat M, Bijvoet OLM, Courpron P, Edouard C, Klenerman L, Neer RM, Renier JC, Slovik D, Vismans FJFE, Potts J (1980) Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. B M J 280:1340–1344
32. Reeve J, Arlot M, Bernat M, Charon S, Edouard C, Slovik D, Vismans J, Meunier PJ (1981) Calcium 47 kinetic measurements of bone turnover compared to bone histomorphometry in osteoporosis: the influence of human parathyroid hormone fragment (hPTH 1-34) therapy. Metab Bone Dis Rel Res 3:23–30
33. Reeve J, Podbesek RD, Price TR, Arlot M, Bartlett C, Deacon AC, Edouard C, Gren JR, Hesp R, Katz D, Tellez M, Zanelli GD, Zanelli JM, Meunier PJ (1984) Studies of a "short-cycle" ADFR regime using parathyroid peptide hPTH 1-34 in idiopathic osteoporosis and in dog model. In: Osteoporosis II; Christiansen C., Arnaud C.D., Nordin B.E.C., Parfitt A.M., Peck W.A., Riggs B.L. (eds). Aalborg Stiftsbogtrykkeri, Copenhagen, Denmark, pp. 567–573
34. Reeve J, Zanelli JM (1986) Parathyroid hormone and bone. Clin Sci 71:231–238
35. Recklinghausen Fv (1891) Die fibröse oder deformierende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen. Festschrift Rudolf Virchow zu seinem 71. Geburtstag; Georg Reimer, Berlin, pp. 1–89
36. Rittinghaus E, Busch U, Prokop M, Delling G, Hesch RD (1987) Increase of vertebral density in osteoporotic patients: combination-therapy with 1-38 hPTH and cyclic addition of calcitonin nasal spray. In: Osteoporosis 1987. Christiansen C., Johansen J.S., Riis B.J. (eds). Osteopress ApS, Copenhagen, Denmark, pp. 888–891
37. Saphier PW, Stamp TCB, Kelsey CR, and Loveridge N (1987) PTH bioactivity in osteoporosis. Bone Min 3:75–83
38. Schenk RK, Olah AJ, Merz WA (1973) Bone cell counts. In: Clinical aspects of metabolic bone disease. Frame B., Parfitt A.M., Duncan H. (eds) Excerpta Medica, Amsterdam, Netherlands, pp. 103–113
39. Slovik DM, Rosenthal DI, Doppelt SH, Daly MA, Murray JA, Neer RM (1985) Reversal of idiopathic osteoporosis by treatment with hPTH (1-34) and 1,25 (OH)2D3. Clin Res 33:444 A (Abstr.)
40. Tam CS, Bayley A, Cross EG, Murray TM, Harrison JE (1982) Increased bone apposition rate in primary hyperparathyroidism: measurements based on short interval labeling of bone. Metabolism 31:759–765
41. Zaidi M, Alam AS, Shankar VS, Bax BE, Moonga BS, Bevis PJ, Pazianas M, Huang CL (1992) A quantitative description of components of in vitro morphometric change in the rat osteoclast model: relationships with cellular function. Eur Biophys J 21:349–355