in vivo *27*: 415-418 (2013)

Circulating PTH, Vitamin D and IGF-I Levels in Relation to Bone Mineral Density in Elderly Women*

FRANCO LUMACHI[1], VALENTINA CAMOZZI[2], PAOLO DORETTO[3], RENATO TOZZOLI[3] and STEFANO M. M. BASSO[4]

Departments of [1]Surgical, Oncological and Gastroenterological Sciences (DiSCOG) and [2]Medicine, University of Padua, School of Medicine, Padova, Italy; [3]Department of Clinical Pathology and [4]Surgery 1, S. Maria degli Angeli Hospital, Pordenone, Italy

Abstract. *Age and reduced bone mineral density (BMD) represent major risk factors for vertebral fracture risk, especially in pos-tmenopausal women, and measurement of BMD is currently considered of value in estimating bone mineralization. BMD correlates with demographics and anthropometric parameters, as well as with several markers of bone metabolism and calcium-regulating hormones, such as leptin, osteoprotegerin, parathyroid hormone (PTH), vitamin D, insulin-like growth factor-I (IGF-I) and sex steroid hormones. The aim of this study was to evaluate the relationship between PTH, 25(OH) vitamin D [25(OH)D], IGF-I and BMD in a selected group of elderly women. Thirty-one post-menopausal women over the age of 65, who were not estrogen, vitamin D or bisphosphonate users and did not have a history of fracture, bone disease or malignancy, were prospectively enrolled in the study. All the patients underwent lumbar spine dual-energy x-ray absorptiometry (DXA) and serum calcium, creatinine, PTH, 25(OH)D and IGF-I measurements. As expected, a weakly-inverse correlation between age and 25(OH)D (R=–0.50, p=0.020), and between BMD and PTH (R=–0.48, p=0.027) was found. There was a strong relationship between IGF-I and BMD (R=0.64, p=0.0016), and between age and IGF-I (R=–0.70, p<0.001), while IGF-I did not correlate with 25(OH)D (R=–0.16, p=0.48) or BMI (R=–0.089, p=0.70). In conclusion, in this selected group of elderly women, we found a strong relationship of increased bone resorption, expressed as BMD, to calcium-regulating hormones PTH and IGF-I, while 25(OH)D and BMI seem to be independent of bone mineralization status.*

Secondary hyperparathyroidism (HPT) is a frequent condition in elderly women that may lead to increased bone resorption. Secondary HPT may also affect up to 50% of patients who underwent successful kidney transplantation, representing the most frequent cause of hypercalcemia in the transplant recipient (1, 2). Age and reduced bone mineral density (BMD) represent major risk factors for vertebral fracture risk, especially in post-menopausal women and measurement of BMD is currently considered of value in estimating bone mineralization (3). BMD correlates with demographics (*i.e.*, age and gender) and anthropometric parameters, such as weight, height and body mass index (BMI), as well as with several markers of bone metabolism and calcium-regulating hormones, such as leptin, osteoprotegerin, parathyroid hormone (PTH), vitamin D, insulin-like growth factor-I (IGF-I) and sex steroid hormones (4-7).

The aim of this study was to investigate the relationship between serum levels of parathyroid hormone (PTH), 25(OH) vitamin D [25(OH)D] and IGF-I, and BMD in a selected group of elderly women who were not estrogen, vitamin D or bisphosphonate users.

Patients and Methods

A group of 31 post-menopausal women over the age of 65 (median age=68 years, range=65-74 years) was prospectively enrolled in the study and informed consent was obtained from each participant. Patients who used bisphosphonates, estrogens, calcium or vitamin D and those who had a history of fracture, bone diseases or malignancy, were excluded from the study. The factors examined were age, age at menarche and menopause, weight, height and body

*Presented at the European Congress on Osteoporosis and Osteoarthritis, International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis & Osteoarthritis (ECCEO12) Joint Meeting, Bordeaux (France), 21-24 March, 2012.

Correspondence to: Professor Franco Lumachi, Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University of Padua, School of Medicine, Via Giustiniani 2, 35128 Padova, Italy. Tel: +39 0498211812, Fax: +39 0498218277, e-mail: flumachi@unipd.it

Key Words: Post-menopausal, elderly, IGF-I, PTH, 25(OH)D, bone mineral density, osteoporosis.

mass index (BMI, calculated as weight in kilograms divided by the square of height in meters). Serum calcium, creatinine, PTH, 25(OH)D and IGF-I measurements were performed in all the patients, who also underwent dual-energy x-ray absorptiometry (DXA, Hologic QDR 4500 C; Whaltham, MA, USA) and subsequently lumbar spine (L2-L4) BMD measurement (8, 9). *In vitro*, a coefficient of variation (CV) of 0.6% (calculated performing 20 scans of the Hologic Anthropometric Spine Phantom) and *in vivo* the CV was 1.2% (calculated performing two lumbar scans in 10 healthy volunteers), as previously reported (10).

Both serum calcium and creatinine were measured spectrophotometrically, by standard laboratory methods. Serum intact PTH was analyzed by an immunometric assay (Intact PTH Bridge; Adaltis, Bologna, Italy), with a detection limit 10 pg/ml, and inter- and intra-assay CV of 4% and 3.5%, respectively. 25(OH)D was determined by a radioimmunoassay (RIA) (25-hydroxyvitamin D 125I RIA kit; DiaSorin, Stillwater, MN, USA), detection limit 1.5 ng/ml, and inter- and intra-assay CV of 9% (10, 11). Serum IGF-I was measured by a immunoradiometric method (IGF-1 kit; Immunotech, Marseille, France), with detection limit 10 μg/l, and inter- and intra-assay CV of 11% and 4%, respectively (12, 13).

The reported data are expressed as mean±standard deviation (SD) and the relationship between pairs of variables was determined using Pearson's correlation coefficient (R) calculation. Each association was considered statistically significant when the *p*-value was less than 0.01.

Results

Table I lists the main parameters recorded for the overall population. There were no hypertensive patients and both serum calcium and creatinine were within the normal range (2.10-2.55 mmol/l and 53-97 μmol/l, respectively) in all patients. As expected, a weakly inverse correlation between age and 25(OH)D (R=–0.50, p=0.020) and between BMD and PTH (R=–0.48, p=0.027) was found (Table II).

There was a strong relationship (R=0.70, p<0.001) between age and IGF-I and an inverse relationship between IGF-I and BMD (Figure 1), while serum IGF-I levels did not correlate with 25(OH)D (R=–0.16, p=0.48) or BMI (R=–0.089, p=0.70).

Discussion

Calcium metabolism mainly depends on the activity of PTH and vitamin D (2). Secondary HPT is the principal mechanism whereby vitamin D deficiency can be involved in the pathogenesis of pathological fractures in the elderly (14). Vitamin D is hydroxylated to 25-hydroxyvitamin D [25(OH)D] and further 1α-hydroxylated to $1,25(OH)_2$ vitamin D (calcitriol), which is under the direct control of PTH (15, 16). It has long been observed that serum 25(OH)D inversely correlates with serum PTH and that under physiological conditions PTH stimulates both bone resorption and formation, although given intermittently for therapeutic purposes it has anabolic effects on the bone (17-19). The measurement of 25(OH)D, which reflects the total body vitamin storage, is currently considered the best clinical indicator describing vitamin D status (15, 16, 20). IGF-I is a polypeptide hormone involved in the regulation of growth and development, also playing a role in carcinogenesis (21-23).

Table I. *Main parameters recorded in the overall population (N=31). Mean±standard deviation (SD).*

	Age (years)	BMI (kg/m^2)	BMD (g/cm^2)	PTH (ng/l)	25(OH)D (nmol/l)	IGF-I (μg/l)
Mean	68.4	25.1	0.790	72.1	48.6	117.4
SD	2.2	2.1	0.058	8.5	19.2	63.1

BMI, Body mass index; BMD, bone mineral density; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; IGF-I, insulin-like growth factor-I.

It is well-known that both BMD and serum concentration of IGF-I decrease with age and that IGF-I should be considered a potential marker of bone loss, changing many years before a decrease of BMD (24). Thus, IGF-I plays an important role in the pathogenesis of osteoporosis, especially in women (14, 25). Studies performed in patients with male idiopathic osteoporosis are controversial, usually showing no relationship between serum IGF-I and BMD (26, 27), or a weak correlation with BMD at the lumbar spine (LS) only and in men younger than 60 years (28, 29). In menopausal women, bone loss proceeds more rapidly in the LS than in the femoral neck (FN) and osteoporosis at the FN is rare in 60-year-old women, whereas, osteoporosis at the LS is not (30, 31).

Our study confirmed previous data reported by Salminen *et al*. (12), showing a positive relationship (p<0.001) between BMD and serum IGF-I in this selected group of elderly women. Both *in vitro* and *in vivo*, IGF-I and PTH have synergistic actions and the anabolic actions of PTH on bone require the presence of IGF-I (32). Low serum levels of IGF-I increase the risk of pathological fractures in post-menopausal women, independently of BMD (24, 33). We found a significant relationship between serum IGF-I and BMD (R=0.64, p=0.0016), but no correlation (p=NS) was found between IGF-I and 25(OH)D.

Conclusion

In this selected group of elderly women, we found a strong relationship of increased bone resorption, expressed as BMD, to calcium-regulating hormones PTH and IGF-I, while BMI and 25(OH)D seem to be independent of bone mineralization status.

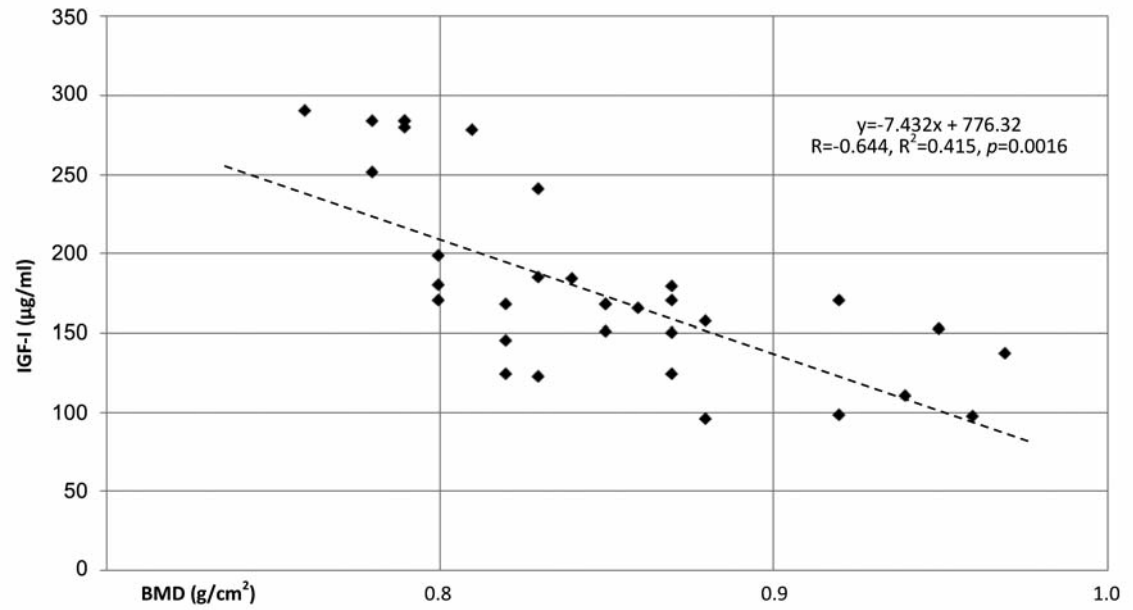

Figure 1. *Relationship between lumbar spine bone mineral density (BMD) and serum insulin-like growth factor-I (IGF-I) levels (N=31).*

Table II. *Analysis of correlations between the main parameters.*

	BMI (kg/m^2)	BMD (g/cm^2)	PTH (ng/l)	25(OH)D (nmol/l)	IGF-I (µg/l)
Age	R=0.192	R=–0.649	R=0.433	R=–0.503	R=0.702
	p=0.403	*p*=0.0014	*p*=0.049	*p*=0.020	*p*<0.001
BMI		R=0.160	R=–0.482	R=–0.094	R=–0.089
		p=0.487	*p*=0.026	*p*=0.686	*p*=0.699
BMD			R=–0.481	R=0.339	R=–0.644
			p=0.027	*p*=0.133	*p*=0.0016
PTH				R=0.039	R=0.495
				p=0.866	*p*=0.026
25(OH)D					R=–0.164
					p=0.477

R, Pearson's correlation coefficient; BMI, body mass index; BMD, bone mineral density; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; IGF-I, insulin-like growth factor-I.

Acknowledgements

We express special thanks to Mrs Francesca Bissolotti for her help in writing of the manuscript and for reviewing the English language.

References

1 Pinho LR, Ribeiro Santos MJ and Pestana Vasconcelos M: Cinacalcet in the treatment of persistent hyperparathyroidism after kidney transplantation. Clin Nephrol *75*: 263-268, 2011.

2 Lumachi F, Motta R, Cecchin D, Ave S, Camozzi V, Basso SM and Luisetto G: Calcium metabolism and hypercalcemia in adults. Curr Med Chem *18*: 3529-3536, 2011.

3 Waterloo S, Nguyen T, Ahmed LA, Center JR, Morseth B, Nguyen ND, Eisman JA, Søgaard AJ and Emaus N: Important risk factors and attributable risk of vertebral fractures in the population-based Tromsø study. BMC Musculoskelet Disord *13*: 163, 2012.

4 Ruhl CE and Everhart JE: Relationship of serum leptin concentration with bone mineral density in the United States population. J Bone Miner Res *17*: 1896-1903, 2002.

5 Kudlacek S, Schneider B, Woloszczuk W, Pietschmann P and Willvonseder R: Serum levels of osteoprotegerin increase with age in a healthy adult population. Bone *32*: 681-686, 2003.

6 García-Pérez MA, Moreno-Mercer J, Tarín JJ and Cano A: Relationship between PTH, sex steroid and bone turnover marker measurements and bone density in recently postmenopausal women. Maturitas *45*: 67-74, 2003.

7 Riggs BL, Khosla S and Melton LJ: Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev *23*: 279-302, 2003.
8 Lumachi F, Camozzi V, Ermani M, Nardi A and Luisetto G: Lumbar spine bone mineral density changes in patients with primary hyperparathyroidism according to age and gender. Ann NY Acad Sci *1117*: 362-366, 2007.
9 Lumachi F, Zanella S, Cella G, Casonato A and Fallo F: Endothelial activation markers soluble E-selectin and von Willebrand factor in primary hyperparathyroidism. In Vivo *25*: 279-282, 2011.
10 Camozzi V, Sanguin F, Albigier N, Scaroni C, Mantero F, Zaninotto M, Frigo A, Piccolo M and Luisetto G: Persistent increase of osteoprotegerin levels after cortisol normalization in patients with Cushing's syndrome. Eur J Endocrinol *162*: 85-90, 2010.
11 Lumachi F, Camozzi V, Tombolan V and Luisetto G: Bone mineral density, osteocalcin, and bone-specific alkaline phosphatase in patients with insulin-dependent diabetes mellitus. Ann NY Acad Sci *1173*: E64-E67, 2009.
12 Salminen H, Sääf M, Ringertz H and Strender LE: The role of IGF-I and IGFBP-1 status and secondary hyperparathyroidism in relation to osteoporosis in elderly Swedish women. Osteoporos Int *19*: 201-209, 2008.
13 Kucera R, Cerna M, Narsanska A, Svobodova S, Strakova M, Vrzalova J, Fuchsova R, Treskova I, Kydlicek T, Treska V, Pecen L, Topolcan O and Pazdiora P: Growth factors and breast tumors, comparison of selected growth factors with traditional tumor markers. Anticancer Res *31*: 4653-4656, 2011.
14 Lips P: Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. Endocrine Rev *22*: 477-501, 2001.
15 Mosekilde L: Vitamin D and the elderly. Clinical Endocrinol *62*: 265-281, 2005.
16 Lumachi F, Cappelletti P, Tozzoli R, Basso SM, Luisetto G and Camozzi V: Diagnosis of alterations of serum calcium metabolism. Med Chem *8*: 551-555, 2012.
17 Lips P, van Ginkel FC, Jongen MJM, Rubertus A, van der Vijgh WJF and Netelenbos JC: Determinants of vitamin D status in patients with hip fracture and elderly control subjects. Am J Clin Nutr *46*: 1005-1010, 1987.
18 Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S and Meunier PJ: Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int *7*: 439-443, 1997.
19 Aslan D, Andersen MD, Gede LB, de Franca TK, Jørgensen SR, Schwarz P and Jørgensen NR: Mechanisms for the bone anabolic effect of parathyroid hormone treatment in humans. Scand J Clin Lab Invest *72*: 14-22, 2012.
20 Eastell R, Arnold A, Brandi ML, Brown EM, D'Amour P, Hanley DA, Rao DS, Rubin MR, Goltzman D, Silverberg SJ, Marx SJ, Peacock M, Mosekilde L, Bouillon R and Lewiecki EM: Diagnosis of asymptomatic primary hyperparathyroidism: Proceedings of the Third International Workshop. J Clin Endocrinol Metab *94*: 340-530, 2009.
21 Kanbur NO, Derman O and Kmik E: The relationships between pubertal development, IGF-I axis, and bone formation in healthy adolescents. J Bone Miner Metab *23*: 76-83, 2005.
22 Schairer C, McCarty CA, Isaacs C, Sue LY, Pollak MN, Berg CD and Ziegler RG: Circulating insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 levels and postmenopausal breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial (PLCO) cohort. Horm Cancer *1*: 100-111, 2010.
23 Lumachi F, Basso SMM and Orlando R: Cytokines, thyroid diseases and thyroid cancer. Cytokine *50*: 229-233, 2010.
24 Liu JM, Zhao HY, Ning G, Chen Y, Zhang LZ, Sun LH, Zhao YJ, Xu MY and Chen JL: IGF-1 as an early marker for low bone mass or osteoporosis in premenopausal and postmenopausal women. J Bone Miner Metab *26*: 159-164, 2008.
25 Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu JL, Ooi GT, Setser J, Frystyk J, Boisclair YR and LeRoith D: Circulating levels of IGF-1 directly regulate bone growth and density. J Clin Invest *110*: 771-781, 2002.
26 Drake WM, Kendler DL, Rosen CJ and Orwoll ES: An investigation of the predictors of bone mineral density and response to therapy with alendronate in osteoporotic men. J Clin Endocrinol Metab *88*: 5759-5765, 2003.
27 Paccou J, Dewailly J and Cortet B: Reduced levels of serum IGF-1 is related to the presence of osteoporotic fractures in male idiopathic osteoporosis. Joint Bone Spine *79*: 78-82, 2012.
28 Gillberg P, Olofsson H, Mallmin H, Blum WF, Ljunghall S and Nilsson AG: Bone mineral density in femoral neck is positively correlated to circulating insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3 in Swedish men. Calcif Tissue Int *70*: 22-29, 2002.
29 Szulc P, Joly-Pharaboz MO, Marchand F and Delmas PD: Insulin-like growth factor I is a determinant of hip bone mineral density in men less than 60 years of age: MINOS study. Calcif Tissue Int *74*: 322-329, 2004.
30 Recker R, Lappe J, Davies K and Heaney R: Characterization of perimenopausal bone loss: A prospective study. J Bone Miner Res *15*: 1965-1973, 2000.
31 Abrahamsen B, Rejnmark L, Nielsen SP, Rud B, Nissen N, Mosekilde L, Bärenholdt O and Jensen JE: Ten-year prediction of osteoporosis from baseline bone mineral density: Development of prognostic thresholds in healthy postmenopausal women. The Danish Osteoporosis Prevention Study. Osteoporos Int *17*: 245-251, 2006.
32 Lombardi G, Di Somma C, Vuolo L, Guerra E, Scarano E and Colao A: Role of IGF-I on PTH effects on bone. J Endocrinol Invest *33(S7)*: 22-26, 2010.
33 Gerneo P, Sornay-Rendu E and Delmas E: Low serum IGF-1 and occurrence of osteoporotic fractures in postmenopausal women. Lancet *355*: 898-899, 2000.

Received January 8, 2013
Revised February 15, 2013
Accepted February 18, 2013