CONCISE REPORT

Relationship of hypovitaminosis D and secondary hyperparathyroidism with bone mineral density among UK resident Indo-Asians

E Serhan, M R Holland

Background:: There is a high prevalence of vitamin D deficiency in UK resident Indo-Asians and this may be complicated by secondary hyperparathyroidism.

Objective: To investigate the relationship between these conditions and bone mineral density (BMD) in Indo-Asian rheumatology patients.

Methods: 110 Indo-Asian patients presenting to a general rheumatology clinic were selected for the study, of whom 77 were vitamin D deficient (HD), and 33 also had associated secondary hyperparathyroidism (HD-SHPT). BMD measurements at the femoral neck (FN), lumbar spine (LS), distal radius (DR), and radius 33% were obtained. T and Z scores were used in the evaluation of the dual energy x ray absorptiometry findings. The Mann-Whitney U test and χ^2 tests were used in the statistical analysis.

Results: The patients with HD-SHPT had significantly lower serum 25-OH-vitamin D, higher serum alkaline phosphatase, and lower calcium levels than the HD group. Both T and Z scores failed to show any significant difference between the groups in the LS, but patients with HD-SHPT compared with those with HD had significantly lower FN T scores (–1.05 (1.47) v 0.28 (1.22), p=0.003), FN Z scores (–0.45 (1.27) v 0.26 (0.96), p=0.001), DR T scores (–1.83 (1.82) v –0.44 (1.77), p<0.001), DR Z scores (–1.25 (1.44) v –0.08 (1.6), p=0.001), radius 33% T scores (–1.65 (1.66) v –0.79 (1.21), p=0.008), and radius 33% Z scores (–1.07 (1.28) v –0.44 (1.1), p=0.017).

Conclusion: Hypovitaminosis D complicated by secondary hyperparathyroidism is associated with significantly decreased bone mineral density.

W e, like others, have demonstrated a high prevalence of hypovitaminosis D (HD) among UK resident Indo-Asians (Asians from the Indian subcontinent).[1] In our previous project we found a prevalence of 56% for HD and 22% for hypovitaminosis D with secondary hyperparathyroidism (HD-SHPT) among the Indo-Asian rheumatology patients.[2] Vitamin D is essential in bone mineralisation and its deficiency leads to loss of bone mineral density (BMD), osteoporosis, and related fractures.[3 4] Surprisingly, no evidence is available concerning the prevalence of osteoporosis among Indo-Asians residing in the UK. Nor is it known if decreased bone density and osteoporosis is associated with HD alone or HD-SHPT.

As far as we know, this study is the first to investigate the relationship between HD with or without SHPT and BMD, and the first to consider this particular at risk group of patients.

PATIENTS AND METHODS

One hundred and ten Indo-Asians, predominantly Punjabis with vitamin D deficiency attending a general rheumatology outpatient clinic were recruited into the study during a period of 18 months. Ninety four (85%) of these were women. With the exception of nine patients who had inflammatory arthritis (four complicated with SHPT), the rest complained of nonspecific musculoskeletal aches and pains. Only four patients, two with inflammatory arthritis and two from the HD-SHPT group without inflammatory arthritis, had significant loss of mobility. Subjects receiving vitamin D supplements or anticonvulsants, pregnant or lactating mothers, those with significant other medical conditions or abnormal biochemical renal or liver function were excluded. Dietary scores were obtained by asking the patients about their meat (1, most days; 2, 2–3 times weekly; 3, once weekly; 4, never) and milk consumption (1, ≥1 pint/day; 2, 1–0.5 pints/day, 3, <0.5 pints/day). In the presence of the already known high prevalence of HD with or without SHPT among Indo-Asians, all patients had their 25-OH-vitamin D and parathyroid hormone (PTH) checked, in addition to routine biochemistry. Serum 25-OH-vitamin D was measured by a ^{125}I radioimmunoassay (lower limit of detection of 1 μg/l, between-assay coefficient of variation 7%) and intact PTH by an immunometric affinity purified polyclonal antibody assay (lower limit of detection of 5 ng/l, between-assay coefficient of variation 10%). Reference ranges for these assays are as follows: serum 25-OH-vitamin D 8.0–60.0 μg/l, PTH 12–72 ng/l, calcium 2.00–2.60 mmol/l, alkaline phosphatase 80–330 IU/l. Patients with a serum vitamin D level of <8.0 μg/l were defined as HD and those with HD and a PTH of >72 ng/l were defined as HD-SHPT.

BMD measurements were made within four to six weeks after the detection of HD and before giving the patients supplementation treatment. Measurements, including both T and Z scores at the femoral neck (FN), lumbar spine (LS), distal radius (DR), and radius 33%, were made with dual energy x ray absorptiometry on a Lunar XL scanner set to match for age, weight, and ethnicity. T scores, advocated by the World Health Organisation were used in the definition of bone densitometry findings.[5] BMD values of not more than 1 SD below the young adult mean value (T>–1.0) were defined as normal, whereas osteopenia was defined as –2.5≤T≤–1.0 and osteoporosis as T<–2.5.

Two groups were compared using the Mann-Whitney U test. The χ^2 test was used to determine the difference between proportions. Statistical tests were considered significant at p<0.025 (two sided). Results are presented as the mean (SD).

RESULTS

The ages of 110 Indo-Asian patients ranged between 20 and 81, with a mean age of 50.8 (12.5). Body mass index was 27.7 (4.7) kg/m^{2}. The serum creatinine, calcium, corrected calcium,

**Table 1** A comparison of Indo-Asian patients with HD and those with HD-SHPT. Results are given as mean (SD)

	Hypovitaminosis D with normal PTH	Hypovitaminosis D with raised PTH	p Value
Number	77	33	
Age years	49 (11.7)	55 (13.2)	0.013
Female (No (%))	67 (87)	27 (82)	NS
BMI (kg/m^2)	27.1 (4.3)	29.0 (5.3)	NS
Meat score	3.1 (1.0)	3.7 (0.5)	0.003
Milk score	2.5 (0.7)	2.6 (0.7)	NS
Creatinine (µmol/l)	91.4 (13)	96.4 (23)	NS
Calcium (mmol/l)	2.36 (0.12)	2.30 (0.12)	0.005
Alkaline phosphatase (IU/l)	179 (57)	361 (642)	0.003
Vitamin D (µg/l)	4.5 (2.1)	3.3 (2.6)	0.008
PTH (ng/l)	40.8 (15.5)	150.6 (145.4)	<0.001
Femoral neck T score	−0.28 (1.22)	−1.05 (1.47)	0.006
Femoral neck Z score	0.26 (0.96)	−0.45 (1.27)	0.001
Lumbar spine T score	−0.67 (1.59)	−1.07 (1.94)	NS
Lumbar spine Z score	−0.67 (1.59)	−1.07 (1.94)	NS
Distal radius T score	−0.44 (1.77)	−1.83 (1.82)	<0.001
Distal radius Z score	−0.08 (1.6)	−1.25 (1.44)	0.001
Distal radius 33% T score	−0.79 (1.21)	−1.65 (1.66)	0.008
Distal radius 33% Z score	−0.44 (1.1)	−1.07 (1.28)	0.017

Figure 1 Receiver operator curve in which osteoporosis is defined as a distal radius T score of <−2.5, for different PTH cut off points.

and alkaline phosphatase levels were 93 (17) µmol/l, 2.34 (0.12) mmol/l, 2.36 (0.11), and 234 (361) IU/l, respectively. None had a serum creatinine or calcium outside the normal range, but in five patients the alkaline phosphatase was raised (357, 396, 703, 1112, 3779 IU/l). The mean serum 25-OH-vitamin D and PTH levels were 4.1 (2.3) µg/l and 73.7 (94.5) ng/l respectively. T and Z scores for the FN, LS, DR, and radius 33% were −0.51 (1.34), −0.05 (1.11), −0.84 (1.69), −0.33 (1.46); −0.86 (1.89), −0.43 (1.64), −1.05 (1.41), −0.63 (1.19), respectively.

We further divided the 110 patients into two groups and table 1 shows these results. Seventy seven (70%) had low 25-OH-vitamin D but normal PTH (HD), and 33 (30%) had both low 25-OH-vitamin D and raised PTH (HD-SHPT). The group with HD-SHPT were older (p=0.013), ate less meat (p=0.003), had higher serum alkaline phosphatase (p=0.003), and lower calcium levels (p=0.005), but no significant differences existed in milk consumption, serum creatinine, or corrected calcium. As might be expected, the HD-SHPT group had a lower 25-OH-vitamin D (p=0.008) and a higher PTH (p<0.001). The HD-SHPT group had significantly lower T and Z scores for FN (T: −1.05 (1.47) v −0.28 (1.22), p=0.006; Z: −0.45 (1.27) v 0.26 (0.96), p=0.001), DR (T: −1.83 (1.82) v −0.44 (1.77), p<0.001; Z: −1.25 (1.44) v −0.08 (1.6), p=0.001), and radius 33% (T: −1.65 (1.66) v −0.79 (1.21), p=0.008; Z: −1.07 (1.28) v −0.44 (1.1), p=0.017). Of the five patients with abnormally raised alkaline phosphatase levels, four were from the HD-SHPT group. Those with raised PTH concentrations tended to vegetarianism (72% v 44%, p=0.003). The overall rates for osteopenia and osteoporosis as defined by T scores were 42% and 28%. When the two groups were analysed separately, we found that the group with HD-SHPT had a significantly higher number of patients with osteoporosis. The rates for osteopenia and osteoporosis were 47% (36/77) and 18% (14/77) in HD patients as compared with 30% (10/33) and 52% (17/33) in HD-SHPT patients (χ^2=7.5, p<0.01).

There was a negative correlation (Deming's linear regression) between PTH and DR T scores in the older HD-SHPT group (r=−0.432). Further analysis using receiver operator curves (ROC) (fig 1), in which those with osteoporosis were defined as having DR T scores below −2.5, showed an optimal value for PTH of 60 ng/l with a sensitivity of 64% and specificity of 67% compared with 50% and 74%, respectively, when the quoted reference range upper limit of 72 ng/l was used.

There was no significant difference in the ratio between the sexes in the two groups (χ^2=0, p>0.5).
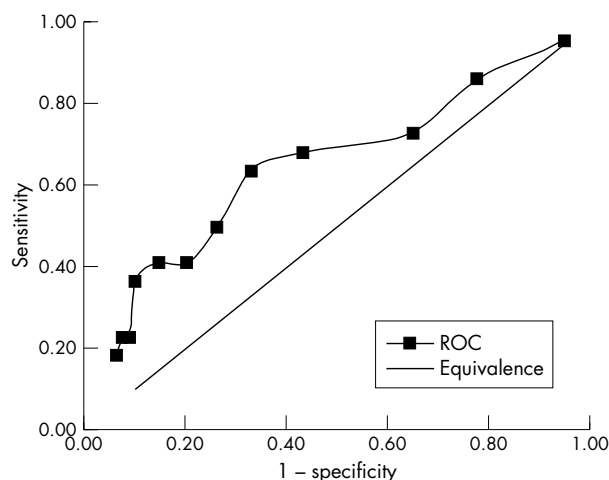
DISCUSSION

Several studies have demonstrated a correlation between low bone mass and prediction of fractures,[6][7] although we are unaware of any study in Indo-Asians. A recent study amongst postmenopausal American women, independent of their oestrogen levels, found lower vitamin D levels, higher PTH concentrations, and higher bone resorption markers in women with fractures.[8] The use of calcium and vitamin D supplements leads to decreased bone loss and decreased incidence of hip fractures,[9] improves BMD at 12 months,[10] and suppresses SHPT due to vitamin D deficiency within three months.[11] Raised PTH levels which are often found in the elderly, if left unchecked, will lead to an increase in bone turnover and consequently result in the loss of bone mass. It is also claimed that in the elderly, HD will lead to decreased intestinal calcium absorption, thus causing SHPT.[12] Bone resorption caused by hyperparathyroidism occurs primarily in endocortical regions and is irreversible.[13]

In the light of this, the known high proportion of Indo-Asians with HD and with SHPT complicating HD is of concern.[2] It raises the possibility that bone health is seriously at risk among Indo-Asians who have depleted 25-OH-vitamin D concentrations. As the original settlers from the Indian subcontinent enter their old age, there is likely to be an increase in the rate of fractures either due to osteoporosis, osteomalacia, or a combination of both.

To our knowledge, this study is the first comparing bone mineral density findings in Indo-Asians according to their vitamin D status and the first to assess the impact of any associated SHPT. The potential influence of SHPT on osteopenia in Asian vegetarian patients was suggested a decade ago using metacarpal cortical thickness.[14] It is well known that in primary hyperparathyroidism, low bone mass occurs as a result of depletion of cortical skeleton as opposed to cancellous bone.[15] Raised PTH levels in our patients were exclusively secondary to HD. With the bone effects of primary hyperparathyroidism in mind, we decided to incorporate the measurement of the distal third of radius (rich in cortical bone), into our bone densitometry studies as well. Cortical bone mass loss was seen in radius 33% and also in the FN, which contains both cortical and cancellous bone. On the other hand, highly significant losses were encountered in the DR, which is mainly made of cancellous bone (fig 2). These findings are suggestive of continuing metabolic bone disease, such as untreated vitamin D deficiency, leading to formation of excess unmineralised osteoid.

The DR data showed that the optimal value for PTH for determining osteoporosis was 60 ng/l (sensitivity 64%, specificity 67%) in contrast with the quoted upper limit of 72 ng/l
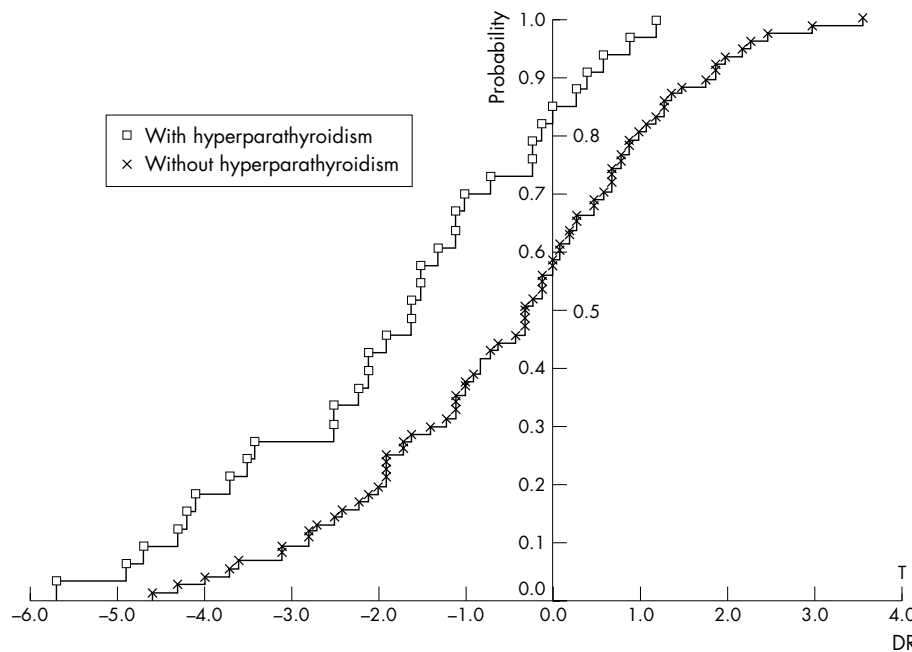
Figure 2 Cumulative probability plots for distal radius bone mineral density T score distribution among Indo-Asian rheumatology patients with hypovitaminosis D associated with hyperparathyroidism (n=33), compared with those without hyperparathyroidism (n=77).

(sensitivity 50%, specificity 74%). This figure of 60 ng/l is also in agreement with ROC studies by Anderson (personal communication, 2001) who was investigating the use of PTH to ascertain the presence of HD.

We discovered no significant difference in the distribution between the two groups. Fifty two (55%) of the women were postmenopausal, 32 in the HD and 20 in the HD-SHPT group ($\chi^2 = 2.64$, p>0.1). Oestrogen, follicle stimulation, and luteinising hormone assays were not done on our female patients. The other osteoporosis risk factors, such as smoking and alcohol had no influence on our patients' bone mass, who were predominantly Punjabi Sikhs and Hindus. Among the subjects entered into the study there were no smokers and no alcohol abuse because of their religious and cultural beliefs. Further to this, men in this group were specifically questioned about their alcohol consumption and smoking habits.

Although large scale epidemiological studies are needed to determine the co-prevalence of osteoporosis with HD with or without SHPT among UK resident Indo-Asians, our data clearly show that HD with SHPT is significantly associated with an adverse outcome for BMD.

The natural history of the progression of HD to the onset of SHPT is unknown and thus unpredictable. In our view, because HD is attended by already reduced BMD, we recommend screening Indo-Asian patients attending rheumatology clinics for their vitamin D status and early intervention with calcium and vitamin D supplements before SHPT occurs.

ACKNOWLEDGEMENTS

····················
Authors' affiliations
E Serhan, Department of Rheumatology, New Cross Hospital, Wolverhampton WV10 0QP, UK
M R Holland, Department of Clinical Chemistry, New Cross Hospital

Correspondence to: Dr E Serhan; e.serhan@btinternet.com

REFERENCES
1 **Finch PJ**, Ang L, Colston KW, Nisbet J, Maxwell JD. Blunted seasonal variation in serum 25-hydroxy vitamin D and increased risk of osteomalacia in vegetarian London Asians. Eur J Clin Nutr 1992;46:509–15.
2 **Serhan E**, Newton P, Ali HH, Walford S, Singh BM. Prevalence of hypovitaminosis D in Indo-Asian patients attending a rheumatology clinic. Bone 1999;25:609–11.
3 **Baker MR**, McDonnell H, Peacock M, Nordin BE. Plasma 25-hydroxy vitamin D concentrations in patients with fractures of the femoral neck. BMJ 1979;i:589.
4 **Cummings SR**, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. Lancet 1993;341:72–5.
5 **WHO**. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organisation, 1994. (WHO technical report series 843.)
6 **Eastell R**. Commentary: Bone density can be used to assess fracture risk. BMJ 1999;318:864–5.
7 **Riggs BL**, Melton LJ III, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. Bone 1996;18:197–201S.
8 **LeBoff MS**, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin d deficiency in postmenopausal US women with acute hip fracture. JAMA 1999;281:1505–11.
9 **Chapuy MC**, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment of three years on hip fracture in elderly women. BMJ 1994;309:108.
10 **Deroisy R**, Collette J, Chevallier T, Breuil V, Reginster JY. Effects of two 1-year calcium and vitamin D$_3$ treatments on bone remodelling markers and femoral bone density in elderly women. Current Therapeutic Research 1998;59:2–14.
11 **Chapuy MC**, Chapuy P, Thomas JL, Hazard MC, Meunier PJ. Biochemical effects of calcium and vitamin D$_3$ supplementation in elderly, institutionalised, vitamin D deficient patients. Rev Rhum Engl Ed 1996;63:135–140.
12 **Eastell R**. Pathogenesis of postmenopausal osteoporosis. In: Primer on the metabolic bone diseases and disorders of mineral metabolism. 4th ed. Philadelphia: Lippincott Williams and Wilkins, 1999:260–2.
13 **Khaw KT**, Sneyd MJ, Compston J. Bone density parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. BMJ 1992;305:273–6.
14 **Fonseca V**, Agnew JE, Nag D, Dandona P. Bone density and cortical thickness in nutritional vitamin D deficiency: effect of secondary hyperparathyroidism. Ann Clin Biochem 1988;25(Pt 3):271–4.
15 **Silverberg SJ**, Shane E, de la Cruz L, Dempster DW, Feldman F, Seldin D, et al. Skeletal disease in primary hyperparathyroidism. J Bone Miner Res 1989;4:283–91.