Quantitative Heel Ultrasonography, 25-Hydroxyvitamin D, and Urine Amino-terminal Cross-linking Telopeptide of Type I Collagen in Patients With a Recent Hip Fracture

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Objective. This study examined quantitative heel ultrasonography (QUS), 25-hydroxyvitamin D (25-OHD) levels, and urine amino-terminal cross-linking telopeptide of type I collagen (NTX-I) levels in patients with a recent osteoporotic hip fracture to see whether they were clinically useful. ***Methods.*** Stiffness index (SI) T scores from QUS, 25-OHD levels, and urine NTX-I levels were obtained in 53 female and 32 male patients with hip fractures. Sixty-five female patients and 5 male patients attending our geriatric clinic were used for comparison. ***Results.*** The SI T scores of the hip fracture patients were less than those of the geriatric clinic patients. The difference was significant in female patients ($P = .0001$) but not in male patients ($P = .1$). Serum levels of 25-OHD were less than 28 ng/mL in 50 of 59 patients and less than 5 ng/mL in 2 patients. Levels of urine NTX-I were variable and were not correlated with other parameters. ***Conclusions.*** Patients who have had a hip fracture have a low SI determined by QUS; this is easy to perform, and it provides a baseline T score from which to assess treatment effects. Most of these patients are vitamin D deficient, and measurement of the 25-OHD level would enable physicians to prescribe an appropriate dose of vitamin D. Urine NTX-I measured shortly after a hip fracture is not clinically helpful. ***Key words:*** age; amino-terminal cross-linking telopeptide of type I collagen; body mass index; heel ultrasonography; hip fracture; 25-hydroxyvitamin D.

Abbreviations
BCE, bone collagen equivalent; BMD, bone mineral density; BMI, body mass index; BUA, broadband ultrasound attenuation; Cr, creatinine; DXA, dual-energy x-ray absorptiometry; NTX-I, amino-terminal cross-linking telopeptide of type I collagen; QUS, quantitative heel ultrasonography; SI, stiffness index; 25-OHD, 25-hydroxyvitamin D

Received November 11, 2008, from St Luke's Roosevelt Hospital and Columbia University, New York, New York USA. Revision requested November 24, 2008. Revised manuscript accepted for publication December 9, 2008.

This study received financial support from the Alliance for Better Health (Procter & Gamble Pharmaceuticals, Inc, and Sanofi-Aventis).

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There is widespread inertia among physicians concerning screening for and treatment of osteoporosis. A survey done in 2000 of 490 physicians in Ontario, Canada, with 275 respondents illustrates this. Ninety-two percent of the respondents were family physicians; 28.7% were caring for more than 100 patients in long-term care. Most (85.8%) saw from 1 to 10 hip fractures yearly in their practices. Half of the respondents estimated the prevalence of osteoporosis to be 40% to 80% among their long-term care patients; 45.5% said that they did not routinely assess their patients for the disease, and 26.8% did not routinely treat it. Half of the physicians (50.9%) would treat patients at high risk on the basis of the clinical history, 47.9% if patients had a vertebral com-

pression fracture on plain radiography, 43.8% if patients were highly functional, 42% if osteoporosis was confirmed with bone mineral densitometry, and 30% if patients had a recent fracture. Perceived barriers to initiating treatment included the cost of therapy, patient or family reluctance to accept therapy, and the time or cost of diagnosis.[1]

Port et al[2] reported a study involving 348 hip fracture patients in which only 18% of women and 8% of men with a prior hip fracture were receiving any specific antiosteoporosis therapy. In a survey of 2804 members of a health maintenance organization consisting of women aged 50 to 89 years and men aged 65 to 89 years who had sustained an osteoporotic fracture, only 4.6% had treatment initiated after the fracture. Women sustained 80.7% of these fractures, but only 8.4% had bone mineral density (BMD) measurements, and only 42.4% of the latter received any treatment during the 2 years of the study.[3]

The reference standard for diagnosing osteoporosis is dual-energy x-ray absorptiometry (DXA), but it cannot be used in the immediate aftermath of a hip fracture because pain prevents patients from lying immobile on a metal table, which this technique requires. When the patients are discharged, their restricted mobility makes it difficult for them to travel to a facility that performs DXA. Prospective studies involving a total of 16,000 patients comparing quantitative heel ultrasonography (QUS) with DXA of the spine, hip, and wrist show that they are similar or identical in their ability to predict osteoporotic fractures of the spine, hip, and wrist.[4–6] We thought that QUS would overcome the difficulties of screening with DXA in this context. Quantitative heel ultrasonography does not require a licensed technician. It is comparatively inexpensive, does not require special training to use, and can be used at bedside. The actual measurement takes 1 minute to perform, and the patient can sit or lie in any comfortable position. These advantages are considerable when compared with DXA.

There is evidence that vitamin D deficiency may contribute to hip fractures,[7–11] and we thought that the simple blood test required for measuring 25-hydroxyvitamin D (25-OHD), a surrogate of vitamin D status, would be a simple and valuable screening procedure in hip fracture patients.

We also explored screening with urine aminoterminal cross-linking telopeptide of type I collagen (NTX-I), an index of bone turnover, because increased bone turnover has been reported to be predictive of osteoporotic fractures.[12,13] However, Gerdhem et al[14] reported that high levels of bone turnover markers predict fractures that engage the trabecular bone, but they did not predict hip fractures.

The objective of this study was to see whether these 3 simple screening tests would provide information for guiding physicians taking care of patients with a hip fracture. To our knowledge, there are no previous reports of QUS or NTX-I measurement after hip fractures, although there are several reports of 25-OHD measurement.

Materials and Methods

The study was approved by the hospital Institutional Review Board. It was conducted from January 2003 until September 2005. All patients gave informed consent. Risks to confidentiality were minimized by coding the patients with numbers rather than with names. The criteria for participation were any woman 50 years or older and any man 60 years or older who had been hospitalized for a hip fracture. Patients who were incompetent were excluded, as were patients with high-energy trauma or pathologic fractures and those who had secondary osteoporosis, eg, hyperparathyroidism, renal failure, nonskin cancer, or bone disease other than osteoporosis. We were informed of admissions for hip fractures by the orthopedic department. Patients were interviewed within 1 to 6 days after fracture repair. Patients were weighed on a chair scale, and they were measured lying supine with a tape measure to the nearest 0.5 in. The body mass index (BMI) was calculated by the formula BMI = weight (kilograms)/height (meters squared).

Serum levels of 25-OHD were measured by a radioimmunoassay (DiaSorin Inc, Stillwater, MN). Sensitivity was measured as 1.5 ng/mL, intra-assay precision as 8.2%, and inter-assay precision as 10.5%, with a laboratory reference range of 9 to 54 ng/mL.

Urine concentrations of NTX-I were measured by a competitive immunoassay (Vitros Immunodiagnostic; Ortho-Clinical Diagnostics, Inc,

Raritan, NJ). Sensitivity was measured as 10 nmol/L bone collagen equivalent (BCE)/mmol/L creatinine (Cr), intra-assay precision as 3.9%, and inter-assay precision as 9.4%. The reference range was 10 to 110 nmol/L BCE/mmol/L Cr in women and 11 to 103 nmol/L BCE/mmol/L Cr in men. As far as possible, a second morning urine sample was obtained for measurement of urine NTX-I.

The stiffness index (SI) was measured in the calcaneus contralateral to the side of the fracture with an Achilles Express ultrasonometer (Lunar Corp, Madison, WI). The measurement was performed with the patient either lying or sitting. The precision of this machine is ±2%. The SI combines both speed of sound (SOS) and broadband ultrasound attenuation (BUA) in the following formula: SI = (0.67 × BUA + 0.28 speed of sound) – 420.[15] The SI is reported as a T score, which is the number of SDs away from the mean T score of the database of 314 women aged 20 to 35 years.[16] No database exists for men; thus, the T score of the men used the same database of women.

Results

Table 1 shows the characteristics of the female hip fracture and office patients. The mean 25-OHD level of the female hip fracture patients with a T score of –2.5 or lower was 20.5 ng/mL, not significantly different from that (18.7 ng/mL) of the hip fracture patients with a T score higher than –2.5 ($P = .68$).

The mean age (81.3 years) of the hip fracture group was older ($P = .0343$) than the mean age (78.3 years) of the office patients. The mean T score of the hip fracture group was –2.5, which was lower ($P = .0001$) than the score of the office group (–1.7).

In female patients, the T score was correlated with BMI (r = 0.41; $P < .001$) and age ($r = –0.31$; $P < .001$). The age/BMI ratio correlated with the T score ($r = –0.44$; $P < .001$). This ratio was significantly different in hip fracture patients versus office patients ($P < .0001$). Thirty-seven female patients had osteoporosis, defined by a T score of –2.5 or lower; 13 had osteopenia, defined by a T score of higher than –2.5 but lower than –1; and 3 had a normal T score, defined as a score of 1 or higher.

Table 2 shows the characteristics of the male hip fracture and office patients. The mean 25-OHD level of the male hip fracture patients with a T score of –2.5 or lower was 13.3 ng/mL, not significantly different from that (17.1 ng/mL) of the hip fracture patients with a T score higher than –2.5 ($P = 0.24$)

The number of male office patients without hip fracture was 5, too small to be a useful comparison group for the 32 hip fracture patients. Thus, there were no statistically significant differences between the male hip fracture patients and the office patients for age and T score; however, there was a statistical trend suggesting that the mean T score for the hip fracture patients was lower than the mean T score for the office patients ($P < .1$). The mean BMI of the male hip fracture patients was 23.8, whereas that of the office patients was 27.1 ($P = .16$). In male patients, the T score did not correlate with BMI ($r = 0.3$; $P = .08$) or age ($r = –0.009$; $P = .96$). The mean age/BMI ratio ± SD in the male hip fracture patients (3.4 ± 0.7) was not

Table 1. Characteristics of Female Hip Fracture and Geriatric Office Patients

Characteristic	n	Fx	SD	n	Ofc	SD	*P* (Fx vs Ofc)
Mean age, y	53	81.3	9.5	65	78.3	7.9	.008
Mean BMI, kg/m^2	53	23.4	5.2	62	28.3	5.9	.0001
Mean age/BMI ratio	53	3.7	0.9	62	2.8	0.7	.00001
Mean T score	53	–2.8	1	65	–1.7	1.1	.0001
Mean 25-OHD, ng/mL	36	19.7	8.8				
Mean NTX-I, nmol/L BCE/mmol/L Cr	32	69.5	40.2				

Serum 25-OHD Levels Categorized by Ranges in Female Fx					
Serum 25-OHD, ng/mL	<5	≥5–10	11–20	21–27	≥28
Fx, n	1	3	15	10	7

Fx indicates hip fracture patients; and Ofc, geriatric office or clinic patients.

Table 2. Characteristics of Male Hip Fracture and Geriatric Office Patients

Characteristic	n	Fx	SD	n	Ofc	SD	*P* (Fx vs Ofc)
Mean age, y	32	79	8.7		77.2	8.9	.68
Mean BMI, kg/m^2	31	23.8	4.1	5	29.3	6	.1560
Mean age/BMI ratio	31	3.4	0.7	5	3.1	1	.3491
Mean T score	32	–2	1.3	5	–0.9	1.5	.10
Mean 25-OHD, ng/mL	23	15.5	7.9				
Mean NTX-I, nmol/L BCE/mmol/L Cr	20	68.2	45.3				
Serum 25-OHD Levels Categorized by Ranges in Male Fx							
Serum 25-OHD, ng/mL	<5	≥5–10	11–20	21–27	≥28		
Fx, n	1	5	13	2	2		

Fx indicates hip fracture patients; and Ofc, geriatric office or clinic patients.

significantly different from that of the office patients (3.1 ± 1; $P = .35$). There was no correlation between the T score and the age/BMI ratio among male patients, although there was a trend ($r = –0.26$; $P = .13$).

Four patients had 25-OHD levels higher than or equal to 32 ng/mL. The mean T score for the female patients was significantly lower ($P = .002$) than the mean T score for the male patients. The mean age (81.3 years) of the female hip fracture patients was higher than the mean age (79 years) of the male hip fracture patients ($P < .07$). There were no other significant differences between the male and female patients.

Among the male hip fracture patients, as among the female patients, there were no correlations between the 25-OHD and NTX-I levels and the T score. Twelve male patients had a T score of –2.5 or lower; 13 had a T score higher than –2.5 but lower than –1; and 7 had a T score of –1 or higher.

Discussion

In our study, the parameter that best discriminated between fracture and no fracture among the female patients was the age/BMI ratio ($P < .00001$). However, this ratio was not significantly different in male patients with and without hip fractures. To our knowledge, there are no previous reports of this ratio as being a predictor of or having an association with osteoporotic fractures, although it is well known that increased age[17] and a decreased BMI[18] are both associated with an increased risk of osteoporotic fractures. The importance of this ratio, which is a function only of the height, weight, and age of the patient, is that it is easily accessible but will still provide better (statistical) prediction of osteoporotic fractures than 25-OHD measurement or QUS in female patients.

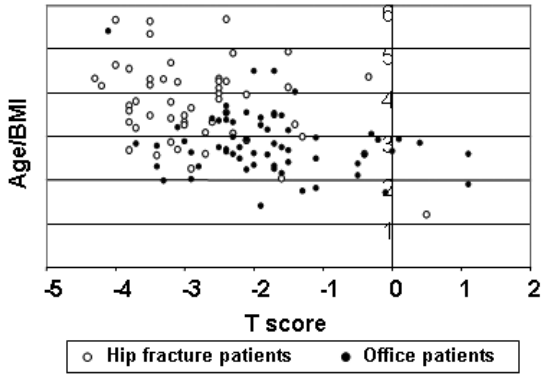
Wildner et al[17] identified 959 postmenopausal women from the National Health and Nutrition Examination Survey III study to assess the relative contribution of risk predictors for low BMD. Age and weight were by far the most informative predictors of low BMD among 20 candidate risk predictors.

Two recent studies agreed that a low BMI is a risk factor for osteoporosis and fractures. A study by Welch et al[18] of more than 15,000 men and women found that the effect of the BMI on the linear regression coefficient of the BMI with BUA was 1.5 times greater in women than in men ($P < .001$); ie, the BMI had a greater effect on the T score and therefore bone mass in women than in men. Welch at al[18] also found that the age-related decline in BUA was 5 times greater in women than in men; they stated that "it is possible that in postmenopausal women, in whom gonadal production of sex hormones is low, endogenous estrogen levels are related to conversion of precursors to estrogen, which occurs in fat cells, so . . . BMI may indicate not just loading forces but also endocrine status." A meta-analysis by De Laet et al[19] of more than 60,000 men and women reported that the risk ratios for osteoporotic fractures per unit change in the BMI were very similar in men and women ($P > .3$). Our findings are a reminder that the combination of advanced age and a low BMI in women signify a high risk of osteoporotic fractures.

To our knowledge, there have been no previous studies of QUS in patients who have had a hip fracture. Although they varied greatly, the T scores of QUS in the female hip fracture patients were significantly lower than those of the nonfracture patients. This can be seen graphically in Figure 1. Previous studies of QUS have focused on T scores for assessment of fracture risk. Our study shows that besides being very simple to obtain, a low T score is indeed associated with fractures. Our data also show that hip fractures occur in patients with osteopenia and those with a normal T score. This indicate that although risk assessment is meaningful for large groups, it is of limited value for individual patients.

For QUS to be as useful as DXA, it needs to be sufficiently sensitive to be able to show responses to treatment for osteoporosis. There are conflicting reports about the usefulness of QUS when used for follow-up. In a study of 18 patients with osteoporosis treated with an antiresorptive agent, Ingle et al[20] found that finger ultrasonography was similar in clinical utility to DXA at the femoral neck for monitoring treatment. In a 4-year longitudinal study, Gonnelli et al[21] compared BMD at the lumbar spine with QUS in 150 menopausal women for monitoring the response to alendronate. They found that the SI showed sensitivity that was only slightly lower than that of BMD. They concluded that although spinal BMD measurement remains the optimal method, QUS and, in particular, the SI seems to be a sensitive tool for monitoring the response to alendronate.[21] Frost et al[22] did a 2-year longitudinal study on 195 postmenopausal women to monitor the response to antiresorptive therapy, comparing QUS with BMD measurements at the lumbar spine, femoral neck, and total hip. They found that calcaneal QUS showed a highly significant response to antiresorptive therapy, but their conclusion was that the precision of QUS was not good enough to allow it to be used for monitoring the response to treatment.[22] Weiss et al[23] found that the QUS T score performed in several skeletal sites increased after treatment of postmenopausal osteoporosis with alendronate. They concluded that peripheral QUS measurements could be used for following skeletal changes in response to alendronate.[23] Therefore, more study is needed for a definitive conclusion regarding the utility of QUS for monitoring osteoporosis management.

Figure 1. Age/BMI ratio versus T score in female patients.



We found that 50 of 59 patients in this study were vitamin D insufficient on the basis of a 25-OHD cut point of 28 ng/mL. Two patients had osteomalacia, defined by a level of less than 5 ng/mL.[11] One of these was an 86-year-old man with a T score of –3.1 and a BMI of 21.2. The other was an 86-year-old woman with a T score of –4 and a BMI of 18.6. In addition to vitamin D deficiency(osteomalacia), these 2 patients had 2 major risk factors for osteoporosis, namely advanced age and a low BMI.

The mean 25-OHD levels of 20.2 and 16.1 ng/mL in the male and female hip fracture patients were somewhat higher than the range of 8.9 to 16 ng/mL found in previous studies of hip fracture patients.[7–11] We do not know whether 25-OHD levels of the free-living population from the same community are the same as those of patients with hip fractures. We also looked at serum albumin levels, which were significantly lower in the patients with hip fractures than the office patients. We have not included the data because serum albumin is a reverse acute-phase reactant, and it has been found that a fracture causes it to decrease.

A recent editorial pointed out that there is currently no standard definition of optimal vitamin D status for the skeleton, but there is a common opinion that the optimal serum 25-OHD level for bone health is between 50 and 80 nmol/L, with 5 of 6 authorities recommending between 70 and 80 nmol/L (equivalent to between 28 and 32 ng/mL).[24] However, the levels that we and others have reported were from one point in time, and it

is not known how they reflect the vitamin D status over an extended period. The same comments apply to previous studies of vitamin D levels in hip fracture patients. 25-Hydroxyvitamin D levels in those who have not had a hip fracture from the same communities as those who have had a hip fracture have not been reported. Levels of 25-OHD among free-living and institutional communities have been lower than the currently recommended threshold mentioned above. It is not known whether there is a fracture threshold for 25-OHD, nor is the relationship known between bone strength and 25-OHD levels in humans. In rats with undetectable levels of 25-OHD, there was a reduction in BMD in the distal tibial trabecular bone; the femoral necks were weaker than those of non–vitamin D-deficient animals.[25] Another way in which vitamin D deficiency may contribute to hip fractures is by causing proximal muscle weakness and a consequent tendency to fall; the threshold level of 25-OHD at which this happens has not been defined.[26]

The studies that show that osteoporotic fractures are less frequent in patients treated with vitamin D[26–28] have also reported 25-OHD levels at one point in time, as have the studies that have reported that vitamin D does not prevent osteoporotic fractures.[29–31] Because it is not known how one measurement of 25-OHD reflects the vitamin D status of an individual over time, these studies may give an incomplete picture of vitamin D sufficiency or insufficiency. In light of current recommendations, however, our study suggests that patients who have had a hip fracture should have their 25-OHD levels measured, and most will require supplementation with vitamin D.

The NTX-I levels in our study showed considerable variation and did not correlate with the 25-OHD levels, T scores, or ages in hip fracture patients. Veitch et al[32] studied several bone markers sequentially after tibial shaft fractures in 18 patients. For the bone resorption marker serum C-telopeptide of type I collagen, there was a decrease of around 40% from the baseline by the third day of the fracture, rising 100% above the baseline by the seventh day and reaching a maximum of 150% of the baseline by 2 weeks after the fracture.[32] These results show the wide fluctuation in bone resorption that occurs during the week after a fracture, which was when we measured urine NTX-I levels in our patients. Thus, measuring bone markers during this time likely reflects the effects of the fracture rather than baseline bone turnover. Even when not used immediately after a fracture, Gillett and Vasikaran[33] reported that urine NTX-I results rarely altered the clinical treatment of patients with osteoporosis.

Limitations of our study were as follows. One limitation was the lack of a control group; however, finding a suitable control group may not have been possible because hip fractures are more common with increasing age, thinness, and malnutrition. Our study would have been improved if we had measured the 25-OHD levels in our geriatric office patients as well as in the hip fracture patients. A nutritional assessment of the hip fracture patients would have been useful, given that previous studies have indicated a significant prevalence of malnutrition in patients with hip fractures.[34] There was no database of young male patients from which to calculate the true T scores of the male patients.

In conclusion, this study showed a high prevalence of vitamin D deficiency in hip fracture patients. The QUS T scores and BMI were significantly lower, whereas age and the age/BMI ratio were significantly higher, among the female hip fracture patients than in patients attending our geriatric clinic. There were similar changes among the male patients, but not all reached statistical significance. There was a wide range of urine NTX-I levels in the hip fracture patients, which may reflect an acute response to the fracture. It is not helpful to measure bone makers in the immediate aftermath of a fracture. A QUS database of young male patients is needed.

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