TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, VOL. 109, 1998

PERIPHERAL BONE DENSITOMETRY: AN OLD FRIEND REVISITED

MICHAEL KLEEREKOPER and DOROTHY A. NELSON (BY INVITATION)

DETROIT, MICHIGAN

INTRODUCTION

In the past decade osteoporosis has been redefined as a disease of low bone mass and increased fracture risk rather than a disease of fractures per se (1). This change resulted from improved technologies for measurement of bone mass and the availability of new therapies documented to improve bone mass and decrease fracture risk. In common with hypertension and hypercholesterolemia, two similar conditions where a measurement predicts risk of an adverse event, only a minority of persons with osteoporosis are currently being detected, with an even smaller proportion on specific therapy. The prevalence of low bone mass (osteopenia) and osteoporosis in the over 50 age-group in the United States has been estimated at 28 million (2) with fewer than 20% of them aware that they are at increased fracture risk. Yet measurement of bone mass predicts fracture risk at least as well as blood pressure predicts brain attack and several fold better than serum cholesterol predicts heart attack (3).

The earliest quantitative determinations of bone mass involved single photon absorptiometry (SPA) of the mid-radius, a skeletal site which is 95% cortical bone and not a site subject to fragility fracture. Nonetheless several studies demonstrated prospectively that radial bone mass measurement did indeed predict the risk of osteoporotic fracture at the more usual sites of the distal radius, spine, and proximal femur (4). It was these early studies with SPA that demonstrated the superiority of bone mass measurement over cholesterol as a predictor of adverse outcome. Nonetheless it was intellectually unsatisfactory to study patients with hip or spine fractures at a site not prone to fracture. To satisfy this intellectual curiosity techniques were developed to measure bone mass at axial (central) skeletal sites. The first technique was dual photon absorptiometry (DPA) of the spine and proximal femur, followed closely by quantitative computed tomography (QCT) of cancellous bone in the lumbar spine. It was not until 1988

From the Department of Internal Medicine, Division of Endocrinology, Wayne State University School of Medicine, UHC-4H, 4201 St. Antoine, Detroit, Michigan, USA 48201.

that today's "gold standard" dual-energy xray absorptiometry (DEXA or DXA) of the forearm, spine, proximal femur, and total body was developed. Prospective studies with these newer technologies confirmed their improved sensitivity over SPA (and DXA of the forearm) with respect to hip fracture prediction but these studies have only been carried out for relatively short-term with older populations (5).

A major concern with central hip and spine DXA is the limited deployment of the technology. Instruments cost $60–150,000 to purchase, clearly more than can be afforded by most primary care providers. Even if funds are available to larger groups, each instrument requires approximately 150 square feet of space for operation. Improved technology has increased the throughput of each instrument such that a technician working full-time can measure hip bone density in some 3–4 patients per hour. Contrast this with available instruments for peripheral bone mass measurement (forearm or heel) that are still costly at $25–50,000, but occupy only 15–20 square feet and can have at least the same throughput, probably a little greater.

As with hypertension and hypercholesterolemia the costs of disease detection for osteoporosis are minimal compared to the costs of long-term therapy. It would not be cost-effective to detect more osteoporosis with a less expensive peripheral technique if that method over-estimated the need for expensive pharmacologic intervention. Knowledge of the relative performance of peripheral versus central densitometry for case detection is crucial to economic decisions concerning deployment of DXA. In this study we report results of bone mass measurement using DXA at the forearm, spine, and proximal femur of white women referred by community physicians for detection of osteoporosis.

METHODS

Subjects

All white women over aged 50 years referred to our Osteoporosis Center since it opened in 1990 form the basis of this report. The center was predominantly a clinical research laboratory and the existence of the facility had not been advertised other than by word of mouth. Women in whom measurements were made following recruiting efforts for clinical research studies and all women enrolled in research studies are excluded from this analysis. The only relevant clinical details obtained at the time of bone mass measurement are birth date, height, weight, and self-identified ethnicity. None of the 545 eligible subjects were excluded from this analysis although for technical reasons (e.g.

previous forearm fracture, prosthetic devices, orthopedic hardware, etc.) not all measurements were available on each subject. The mean age of the women was 65.2 ± 8.8 years, their mean height 159.0 ± 7.1 cm, mean weight 63.8 ± 12.0 Kg, and mean BMI 25.3 ± 4.4 Kg/m^2.

Bone mineral density (BMD)

Bone mineral content (BMC expressed as grams) and the area of the measurement site (cm^2) were measured on an Hologic QDR 1000W (Hologic Inc., Waltham, MA) using the manufacturer's specifications without change. BMD was calculated as mass/area (g/cm^2) and results compared to reference data provided by the manufacturer. The reference data for the forearm and lumbar spine were obtained by the manufacturer. The reference data for the proximal femur was that obtained during NHANES III (2). For each subject the results were expressed as standard deviation units from the mean value for BMD in young normal white females (T-score). Using the criteria developed by the World Health Organization (6) women were categorized for each skeletal site as being normal ($+1 < T \geq -1$), having low bone mass ($-1 < T > -2.5$), or having osteoporosis ($T \leq -2.5$).

RESULTS

Bone mineral density was normal at all measurement sites in only 47 women (8.7%) suggesting that referring physicians are selecting patients for BMD measurement based on their assessment of the patient's risk and not simply for screening purposes. Osteoporosis at one or more sites was present in 287 women (53.3%) while the remaining 203 women (37.7%) had osteopenia at one or more measurement sites. The women with osteoporosis were older, shorter, and weighed less than those without osteoporosis (Table 1), again consistent with

TABLE 1
Demographics of Subjects with Normal Bone Mineral Density (BMD), Low Bone Mass, and Osteoporosis

Variable	Normal BMD (n = 47)	Low Bone Mass (n = 203)	Osteoporosis (n = 287)	p
Age (yrs)	57.9 ± 6.9	62.6 ± 7.8	68.2 ± 8.4	<0.001[a]
Weight (kg)	72.6 ± 11.7	66.4 ± 11.6	60.3 ± 11.1	<0.001[a]
Height (cm)	163.4 ± 4.5	161.2 ± 6.1	156.6 ± 7.3	<0.001[b]
BMI (kg/m^2)	27.2 ± 4.5	25.7 ± 4.5	24.6 ± 4.1	<0.001[b]

[a] All pairwise comparisons different, $p < 0.05$.
[b] Osteoporotic vs normal and low bone mass, $p < 0.05$.

physician selection of patients for measurement based on putative risk factors for osteoporosis. The prevalence of osteoporosis in our youngest age group (50–59) varied from 12.5% at the forearm to 20.6% at the spine with the two hip sites demonstrating a 13.1% (total hip) and 14.4% (femoral neck) prevalence.

No single measurement site detected every patient with osteoporosis. Of the 287 with osteoporosis at one or more sites, 72% would have been correctly identified if the only measurement site was the forearm. At the lumbar spine and femoral neck 65% would have been detected, while only 54% would have been detected if the only measurement site was the total proximal femur.

Importantly, if only a single measurement site was used, those women identified with osteoporosis were unlikely to have normal BMD at the other measurement sites (Table 2). The major source of misclassification error was most likely the presence of osteophytes in the lumbar spine.

TABLE 2

Percentage of women who had osteoporosis at one or more sites but who have normal bone density at another site

Skeletal Site	Radial Shaft	L2–L4	Total Hip	Femoral Neck
Radial shaft	—	9.2	4.4	2.9
L2–L4	4.9	—	1.6	1.1
Total hip	1.9	1.9	—	0.0
Femoral neck	3.3	7.1	0.0	—

DISCUSSION

There are several issues raised by these data. Firstly in this "enriched" population of patients referred because they or their physicians were concerned about osteoporosis, the yield of abnormal results was remarkably high with only 9% of the women having normal bone mass. This high yield would suggest that at this relatively early period with respect to detection of osteoporosis, physicians are focusing on those women in their practices who have presumed increased likelihood of osteoporosis on the basis of known risk factors. We have no means of ascertaining from this study how many women in these practices have low bone mass or osteoporosis without presumed risk factors.

Our findings are similar to two recent population studies comparing peripheral and central BMD in population studies (6,7). Melton (6) established reference data in 48 healthy premenopausal women in Rochester, Minnesota, and subsequently found an overall prevalence of osteoporosis of 30% in postmenopausal women from the same commu-

nity. Our prevalence data are higher than those Melton obtained for the same age group in the general population. In both studies the prevalence increased with each decade (Figure 1). Both our data and that of Melton demonstrated that no single measurement site was able to detect osteoporosis in each patient and that there was little difference in the detection rate between the sites. The data reported by Melton did not permit an analysis of misclassification.

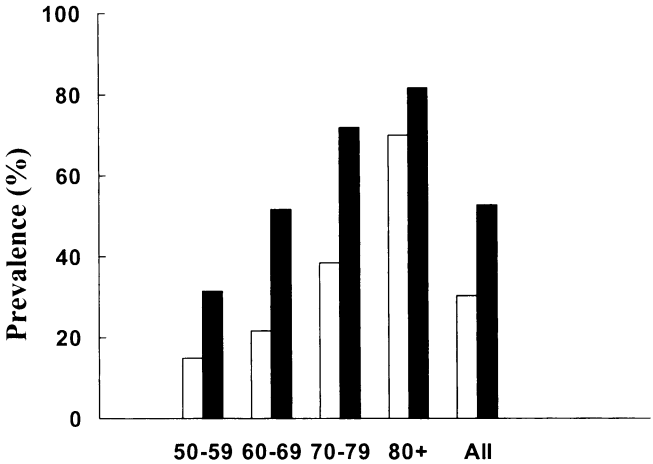

FIG. 1. Prevalence of osteoporosis in a population randomly selected from the community □ and from a population referred specifically for BMD measurement ■.

Arlot et al. (7) obtained reference data for peak adult bone mass from 479 healthy premenopausal women in Lyon, France and established the prevalence of osteoporosis in a postmenopausal population from the same community. In contrast to our data and that of Melton, they found a substantially greater prevalence of osteoporosis detected with a forearm measurement (46%) compared to a femoral neck measurement (12%). Misclassification was defined as the presence of osteoporosis (T score < -2.5) at one site with normal BMD (T score > 1.0) at another site. It was this method we used in our study. They found that no patient classified as osteoporosis at the femoral neck was normal at the radius, but 12% classified as having osteoporosis at the radius were normal at the femoral neck. All this misclassification could be accounted for by the difference in variance around the mean value for peak adult bone mass in the premenopausal population. That value was twice as great at the femoral neck as it was at the radius. There are two important, not mutually exclusive, explanations for this observation. Firstly there may indeed be a smaller population variance

with respect to cortical bone, which comprises 95% of the bone contributing to BMD at the forearm site. Secondly the method's imprecision is substantially greater for femoral neck measurement of BMD (~2.5%) than midradius BMD (~1%). This observation underscores the absolute necessity for optimizing quality control in any osteoporosis screening program. The precision errors just mentioned are derived from clinical research studies in select programs and are substantially better than those obtained in screening programs (8). It also highlights the need for establishing a uniform database for peak adult BMD in the United States. In the three studies discussed in this paper, different reference databases were used. Our own data were all established using one instrument from one manufacturer. Each manufacturer of DXA equipment currently uses a self-generated database which is included in the software distributed with each instrument. Full details of the populations contributing to these databases have not been published in the peer-review literature. Recently all manufacturers have agreed to use the proximal femur data derived from the NHANES III study which should obviate any problem at this site in the near future.

Differences in studies notwithstanding, none were able to detect any performance differences in the detection of low bone mass or osteoporosis between the skeletal sites examined. Clearly, the more skeletal sites are evaluated in an individual patient, the more likely the diagnosis of osteoporosis would be established. If the sole purpose of measuring BMD is to correctly categorize individual patients as being normal, having low bone mass, or having osteoporosis, it is imperative that BMD be measured by an instrument capable of obtaining measurements at multiple skeletal sites including both central and peripheral regions. If BMD measurement was ordered by the community physicians for the purpose of making Yes/No decisions concerning intervention, it would appear that the clinical utility of peripheral measurements is equal to that of central measurements.

This has important public health implications since it suggests that a major effort should be launched to deploy the smaller, less expensive, portable technology as widely as possible. These instruments would be affordable to many more primary care physicians, the main group to be responsible for a disease as prevalent as osteoporosis. For hypertension, hypercholesterolemia, and osteoporosis the cost of disease detection is small relative to the cost of therapeutic intervention once disease is detected. These factors must be considered in developing policies for screening.

The community-based data of Melton (6) indicated that the prevalence of osteoporosis in the 50–59 year old postmenopausal group was

15%, clearly a prevalence too low to make screening a rational choice. By age 80 the prevalence was 70%, again making it difficult to justify screening. In the 60–69 and 70–79 age groups the prevalences were 22 and 39% respectively. It would seem that this is then the most appropriate age group (60–79) for implementing screening programs. We would recommend that all healthy white women have at least one BMD measurement during this period, preferably earlier rather than latter.

The cost per bone density study is substantially less for peripheral measurements than for central measurements. Several entrepreneurial ventures have already taken advantage of this. Peripheral densitometry is available in several communities in pharmacies and in mobile vans. These facilities are offering BMD measurement at a price less than $50 with many programs depending on direct payment by the person having the study without involvement of medical insurance programs. Such programs, similar to blood pressure monitoring at non-medical facilities, home glucose monitoring, home cholesterol measurement, make sense if conducted properly and ethically. This involves the employment of a quality control program and some prescreening of potential participants such that those in whom the measurement will not alter clinical decision making (premenopausal healthy women, those already on therapy, etc.) are discouraged or precluded from participating. Of greatest importance is that there is a physician involved in both the reporting of the results and the receipt of the results. It is inappropriate to provide results directly to the subject without ensuring that her or his physician also receives a copy of the result. Measurement of BMD is the single best predictor of fracture risk, but is by no means the only determinant of fracture risk. Given the limited state of public awareness of osteoporosis, its detection and management, the physician must remain involved in patient care for osteoporosis. This is of course true for other public-access medical technology.

Regulations in several states concerning the deployment of xray-based medical technology also limit the use of peripheral DXA, both in the doctor's office and in non-traditional sites. Those states that still require any xray-based medical technology to be performed by a certified radiology technician will need to be made aware of the very limited radiation exposure with DXA which is not detectably more than background radiation (9). Unless this regulation is modified, primary care physicians cannot be expected to invest in equipment that will also require them to invest in a certified radiology technician. Restricting DXA technology to radiology suites may result in an "out of

sight out of mind" approach to osteoporosis detection. Other states do not generally permit radiologic procedures to be performed on the basis of standing orders, requiring each study to be performed only with an individual request from a physician or other health care provider. One important exception to this is mammography, in which case women can arrange for their own studies to be performed at many centers, including those located in non-traditional settings such as department stores. It is likely that only a strong lobby from women directly will effect a change in these state regulations and that osteoporosis detection will remain limited for some time yet. Given the ease, accuracy, and precision of the methods, as well as the effectiveness of available therapy, this would be an unfortunate delay in an important public health issue.

Future technology will eventually circumvent some of these problems with the recent FDA approval of an ultrasound instrument for detection of bone "strength" in the heel with fracture prediction similar to that obtained with peripheral DXA methods (10). However studies such as those we have reported here have not yet been completed for this new technology, and the problem of standing orders will still need to be overcome.

SUMMARY AND CONCLUSIONS

The earliest assessments of bone "mass" involved metacarpal morphometry that provided insight into age-related changes, the effects of low habitual dietary calcium intake, and the effects of estrogen deficiency and replacement. Single photon absorptiometry (SPA) made quantitative mass measurement possible but this was intellectually unsatisfactory since osteoporotic fractures are more of a concern at the spine and hip than at the wrist. Necessity forced the development of axial bone mass measurement (dual photon absorptiometry-DPA, dual energy xray absorptiometry-DXA, quantitative computed tomography-QCT). Hip measurements provide a better prediction of hip fracture risk than measurements at any other skeletal site. For every standard deviation decrement of bone mass at the hip, relative risk of fracture is 3.0. At non-hip sites the relative risk is only 2.0 for each standard deviation decrement in bone mass. However measurements at non-hip sites provide a fracture risk prediction that is at least the equal of blood pressure measurement for predicting risk of CVA, and substantially better than the risk assessment of acute MI afforded by cholesterol measurement. An important caveat of the superiority of hip measurement is that the data are derived from short-term studies in older

women (>70 years). The relative risk data from phalangeal, forearm, and heel measurements have all been obtained from longer-term studies in younger women.

From a community health perspective, bone density measurements, no matter how accurate, precise, and meaningful, have limited value if access to the technology is limited. Peripheral measurements can be obtained on existing radiographic equipment (phalanges), or small, portable, inexpensive dedicated equipment (forearm, heel). This technology is more likely to make it to the office of the primary care physician than the larger, more expensive, dedicated equipment needed for hip measurements. The peripheral measurement technology is also suitable for high traffic areas, just as blood pressure and cholesterol measurements are widely available. This presentation reviewed the scientific validity of peripheral bone mass measurement and explored the potential for making this technology available at non-traditional facilities such as pharmacies, shopping malls, health clubs, etc.

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DISCUSSION

Bransome, Augusta: When you are defining osteoporosis by decreased bone density, you are actually looking at a surrogate marker and that leads to a question. You are

trying to avoid fractures and you are trying to estimate fracture risk, but according to my somewhat remote understanding, since I'm not a bone disease person, there is a disconnect between bone density and fracture at the various sites. In-as-much as you are using a two-dimensional method to assess a three-dimensional problem, you have the connectivity of bone and resilience of bone which correlates with bone density but are not described by bone density. There are two questions. First, are there efforts to measure the three-dimensional integrity of bone now afoot? Second question, if those are successful, shouldn't that new method be your reference method for comparing single-site cases?

Kleerekoper: You're right, that what we used to measure bone density is a very poor choice of words. We are looking at two-dimensional aerial density, yet everywhere else but in the bone field, density has a three-dimensional component. That is true, but if you go back to my second slide, even the crude measurement that we have, accepting that it is crude, does predict fracture risk extremely well, better by a factor of three than cholesterol, as a single measurement, predicts cardiovascular event. Now, when we have better technology that is more widely applicable, we will all most certainly get better results. The hip clearly gives a better result than the forearm; that is not a surprise. The hip is just not available. One can measure three-dimensional bone density by quantitative computer tomography, which has about 400 times the radiation exposure and something like three or four-fold cost per study and almost an order of magnitude more cost per equipment. Certainly one can do that. The heel densitometry that is currently under advisement by the FDA will have a look at some measure of "quantity or quality" and, you're right, as we get better technology we need to employ the better technology, but we need to find that mix between having the best technology and technology that is deployable. Having fabulous technology where nobody has access is great for an HMO, but it is not particularly good for the community.

Allen, Charleston: The well recognized association between age and the frequency of osteoporosis however measured, suggests two somewhat iconoclastic explanations. One is that osteoporosis is directly associated as a causal factor in longevity. The other is that it is indirectly associated with the promotion of longevity through its association with physiologic factors or body habitus as things that promote that enviable state. I wonder if you'd comment on those possibilities?

Kleerekoper: Certainly, osteoporosis is a function of longevity. If we live long enough, we will all get osteoporosis. One of the things that makes osteoporosis important now is that public health measures this century have clearly dramatically increased life expectancy. Life expectancy of a woman at the time of Christ, as I understand it, was about 21 years. Life expectancy of a woman born at the turn of the century was about 60 years, ten years postmenopause; so we don't worry about postmenopausal problems. But life expectancy of girls born as I am talking to you now is close to 80 years, so that they have 30 years in the postmenopausal stage, 30 years to be at increased risk for osteoporosis. You are absolutely correct, this is a disease of longevity. If you get rid of longevity, we will get rid of osteoporosis and a lot of other things as well.

Santen, Charlottesville: Michael, the prevalence or the specificity and sensitivity of any screening test depends on the prevalence in the population. We have a lot of risk factors for osteoporosis, such as Caucasian race, thinness, family history, etc. Are there subgroups of individuals in which the risk factors are substantially high to eliminate the need to screen or sufficiently low to mandate it?

Kleerekoper: Yes, the data that I presented are exclusively currently for white females. We need to get such data for males and for other ethnic groups of females. For example, the prevalence being 70% in the 80-year old population tells you that you do not need to do a measurement to screen. Likewise, the prevalence in the premenopausal woman is so low that one shouldn't be measuring bone mineral density in a premeno-

pausal woman. The prevalence in those on steroids is extremely high, particularly when one also considers the disease for which they are given and duration of the dose of the steroids, so that one doesn't need to approach them to screen. If we just take the large segment of community that we have as it is, I don't think there is enough within there to say, "gee, you are overweight; therefore, you don't need to have a bone density test; if you are underweight, you do need to have a bone density test." If we applied those rules, for example, to hypertension and hypercholesterolemia, we would still miss too many. I think we need to take exactly the same paradigms for this disease as we do for those two diseases.

Johnston, Indianapolis: I make two points. Independent risk factors, independent of bone mass, can be helpful. We do not have risk factors that allow us to tell what the bone mass would be without measuring it, but there are independent risk factors which estimate fracture risk. I would particularly point out that a history of previous fracture doubles your risk of a subsequent fracture, independent of your bone mass. A family history of hip fracture again doubles your risk, independent of your bone mass, as well as low body weight, and probably smoking. Those risk factors can be important in making a decision about whom to measure, and particularly about whom to screen and whom to treat.

The other point has to do with when you intervene, the yes/no decision. If you have an individual who is three standard deviations below the mean of young normal with a fairly marked decrease in the radius versus the same decrease at the hip, the relative risk of a subsequent fracture of the hip is about 6 for the radius measurement and about 18 for the hip measurement. If a patient with no risk factors has a 2.5 standard deviation decrease, the relative risk is about 13 or 15. So, if the patient is 3 standard deviations down at the wrist with no risk factors, you do not necessarily have to treat; whereas, if it is at the hip you would clearly want to. That is because prevention of hip fractures is what really drives treatment of osteoporosis. Hip fractures are what cause the disability and the cost of the illness.

Kleerekoper: Conrad, the premise of my discussion was not that the forearm was better than the hip. The underlying premise is that the hip is the best site to measure, but it is just not accessible with only 3,000 instruments nationwide. If we can improve that, yes, we can go away and I don't need any sorrow for a good test. That is the first principle and we have no difference there. In terms of the risk factors, I think you are correct with one caveat. Most of the data on risk factor analysis come from older populations. Lots of it comes from the study of osteoporotic fractures. This is a wonderful study of 9700 women, average age 73, then treated. That doesn't relate very well to the woman who enters menopause or the woman who is 55 or 60. When we get that data long-term, I will be more than happy to substitute it. For now, I still have some concerns.