LUNAR®
NEWS

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FROM THE LEADER IN BONE MEASUREMENT

LUNAR Densitometry Provides Low Radiation Dose

LUNAR bone densitometers have been designed to be dose-efficient. Both the pencil-beam DPX® series and the fan-beam *EXPERT®-XL* have a lower radiation dose than competitive products. First, several studies have shown that K-edge bone densitometers are inherently 3X more dose-efficient than those using switched energies [1,2]. The dose with the DPX-IQ™ at 3000μA is ~3 mrem versus 6 to 7 mrem for the QDR-1000 [3,4]. This same advantage is seen for the fan-beam *EXPERT-XL.* In general, fan-beam densitometers have a dose 5X to 10X higher than that required for a comparable determination with a pencil-beam instrument (see Table 1) [3-6]. The dose is usually not important; the dose is low compared to radiographs or computed tomography, even with the highest exposure of fan-beam systems. Eiken et al [3] reported that the actual dose with the QDR-1000 and 2000 was twice that reported by the manufacturer. The DPX, which is 3 to 5X faster than the QDR-1000, has half the dose.

Results for the first *EXPERT* devices [7], which have been quoted by Hologic [8], are for an older system with a lower efficiency detector and a 40-second spine scan. These systems were upgraded to the high-efficiency *EXPERT-XL* two years ago allowing a 6-second scan with lower dose (25 mrem). The dose rate calculated per unit time, such as the rates calculated by Patel et al [8], are biased by the fact that the dose duration on the *EXPERT-XL* is 10X shorter than a QDR-4500 determination and 20X shorter than a QDR-2000 determination.

Fan-beam densitometry has potential advantages over pencil-beam in two regards: (1) speed, and (2) spatial resolution. The 6-second densitometry scan of the *EXPERT-XL* is 12X to 20X faster than other densitometers, and it has 3X better spatial resolution (0.6 versus 1.5 to 2.0 mm). The disadvantages are the aforesaid higher dose, and in addition, the dependence of scan results on position in the beam. The latter is not important for the *EXPERT-XL* which has 3X lower position dependence than the QDR-2000 or QDR-4500 [9,10].

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Table 1. Fan-beam densitometers have higher dose than pencil-beam.

	Pencil-Beam		Fan-Beam		
	DPX-IQ	QDR-1000 [3,4]	*EXPERT-XL*	QDR-2000+ [3,6]	QDR-4500 [4,8]
Time (sec)	70-120	360	6	130	70
Dose (mrem)	3	6-7	26	30	30

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Physical Activity and Bone

There are major effects of physical activity on the skeleton as well as muscle during growth and development [1,2]. High loading activity, like gymnastics, has a particularly strong effect, while swimming does not [3]. This hypertrophy may persist into adulthood, and ultimately could be protective [4-6]. Bradney et al [7] reported that 36 female gymnasts at age 25 had 5 to 15% higher BMD than controls even though they had retired from gymnastics 8 years earlier.

It is relatively easy to demonstrate the effects of activity, and of disuse, on bone under experimental conditions [8-11], but almost all studies in normal adults and the elderly show little effect, if any, of increased activity on bone [12-15]. Even the extensive loading activity of elite gymnastics (30 hours/week over 6 months) increased spine BMD by only 1% in adults and had no effect on femur BMD [16]. Sustained activity does produce muscle hypertrophy and increases strength [14-17], and this may help prevent fractures. On the other hand, excessive exercise can produce amenorrhea with bone loss similar to that following the menopause [18,19]. Training does increase both bone turnover and BMD in adults who have lost bone due to immobilization [20].

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Body Composition By DEXA: Pencil-Beam Preferred

Body composition is becoming of increasing interest for biomedical research, and even clinical practice (see *LunarNews*, April 1996 and July 1996) [1]. The availability of 7000 DEXA scanners, of which approximately half provide total body capability, makes the evaluation of total body bone mineral, and soft tissue quantitation, readily available. Scans take only 8 to 10 minutes with advanced pencil-beam systems; pencil-beam is preferred for accurate tissue quantitation. Studies with the QDR-2000 have shown significant errors in fan-beam measurement of bone mineral content and body fat compared to pencil-beam determinations with the same instrument [2]. Nearly all body composition experts use pencil-beam determinations, and all clinical trials today specify pencil-beam for total body measurement.

Many of the investigators interested in bone have begun to look at composition in relation to the influence of fat and muscle on bone accretion during growth development, and bone loss during aging [3,4].

Changes in total body and regional composition during growth have been well-validated using DEXA measurements of pigs [5,6]. A recent study by Pintauro et al [6] demonstrated excellent correlations with fat and lean components in pig carcasses within the pediatric weight range of 15 to 35 kg. Results are shown in Table 1. The development stages in fat distribution are of pediatric interest [7-9]. Changes of fat distribution with aging are relevant to glucose metabolism, insulin resistance, leptin concentrations, and cardiovascular risk [10-14]. DEXA measurements of the spine, not just total body scans, provide regional body composition across the abdomen, which may be of interest [14-16].

It has been evident for the past 6 years that DPX measurements provide accurate indications of soft-tissue composition. This has been validated on meat samples and animal carcasses, as well as *in vivo*. Local physiological changes of soft-tissue mass and composition can be determined fairly well. However, placement of packets of lard, meat, or water over regions of the body inevitably will result in errors [17] because these are inappropriate models and should not be used for testing of DEXA scans. Bad testing results in bad results.

DEXA offers advantages over many conventional methods of composition analysis because it does not make assumptions with regard to the mineral content or water content of fat-free mass. The mineral content is directly measured, and variations of the water content have virtually no influence on the attenuation coefficient of lean tissue, and hence, do not alter compositional estimates. In normal subjects, mineral constitutes from 5% to 8% of the fat-free mass, and water constitutes 68% to 78% of fat-free mass [18,19]. This variation precludes accurate assessment of body composition by underwater weighing; it simply is too inaccurate to be used by itself to indicate composition. Most researchers using noninvasive approaches concentrate on multi-compartment models using DEXA, underwater weighing, K-40, and total body water. These so-called 3- and 4-compartment models provide more reliable estimates [20,21].

Traditional body composition methods are inaccurate given abnormal hydration, for example, in dialysis patients. Several studies have shown that DEXA can accurately monitor changes of 1 or 2 kg in body fluids occurring with dialysis. Three recent studies (Woodrow et al [22], Abrahamsen et al [23], and Lands et al [24]) confirm earlier studies [25-27]. In general, these fluid shifts are seen as a change in the mass of the lean-tissue component; the mass of body fat and bone is not influenced [22-27].

There are alternate noninvasive measurements which have gained some popularity, or notoriety, depending on one's knowledge. Bioimpedance analysis (BIA) is one simple approach of approximating composition by measuring the skin resistance between the arm and the leg [28-33]. An NIH Technology Assessment Conference on BIA held two years ago concluded that there were not well-defined standards for the instruments or procedures [31]. Hence, it is difficult to assess composition even for grouped data in normal subjects. Moreover, the measurement of resistance by BIA correlates poorly with body composition, and is even more poorly associated (r~0.3) with relatively large changes of fluid content [23]. DEXA, rather than BIA, must be used in clinical patients, particularly those who have fluid alterations.

Clinical use of total body scans for both bone and soft tissue is developing rapidly with the approval of new drugs to produce weight loss. It is important to monitor patients to ensure that this loss does not affect bone or muscle. On the other hand, new studies are showing that treatment with androgens or growth hormone can increase bone and muscle mass, and decrease fat mass [34-37].

Table 1. Comparison of chemical analysis and DPX results in small pigs [6].

	Chemical	DPX	r	SEE (g)
Weight (kg)	25.51	25.44	>0.99	230
Lean Tissue (kg)	19.76	19.23	0.98	670
Fat Tissue (kg)	4.98	5.51	0.98	530
Mineral Mass (g)	780	700	0.94	60

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Calcium: Myth and Reality

Calcium proponents have propagated the myths that (a) increased intake during skeletal growth will increase peak BMD, and (b) supplementation of the elderly will stop osteoporosis [1]. There is a smidgeon of truth here that encourages the reckless and deludes the gullible. An increased calcium intake during growth and development could theoretically increase peak bone mass which presumably could decrease the risk of fracture later in life [2]. Several studies have shown that calcium supplementation in children increases BMD by a few percent [3]; this amounts to a few month's acceleration of growth, not a permanent increase in peak bone mass. Until recently, all supplementation studies were limited in duration; longer studies now show that when supplementation is stopped, the children rapidly revert to the same BMD level as their peers [4,5]. Adequate calcium intake is necessary during growth and development, but there appears to be no reason to supplement children having normal intake.

Vitamin D alone, or given with calcium, suppresses bone turnover in that subgroup of the elderly that have mild secondary hyperparathyroidism [6-8]. About 800 IU of vitamin D is just as effective as potent bisphosphonates in returning bone turnover to normal levels. Hundreds of clinical studies, however, have shown that calcium, while having a slight effect on reducing bone loss in the elderly, does not decrease fracture rates. Several large-scale epidemiologic studies have shown that high calcium intake doubles or triples the risk of hip fracture [9,10]. It has been difficult until recently to reconcile this with retrospective case-control studies that suggest fracture patients have a low calcium intake. Michaelson et al [11], however, reported a relevant prospective study of 65,000 Swedish women of which 123 had an incident hip fracture. The women with hip fracture reported a high calcium intake pre-fracture but reported a low dietary intake post-fracture. Risk of hip fracture was increased three-fold for high dietary intake of calcium and reduced to 0.6 to 0.9 by post-fracture under-reporting of calcium intake. In other words, the apparent effect of a high calcium intake on hip fracture was not only disguised, but actually reversed. The mechanism whereby calcium increases risk of hip fracture remains unclear, but calcium could turn off vitamin D. An alternative to supplementation for those who wish to reduce the risk of hip fracture (and to avoid the side effects of flatulence and constipation) could be to enhance absorption with vitamin D, or to diminish calcium excretion by reducing sodium intake [12-14]. A defect in renal conservation of calcium was proposed as a mechanism for bone loss in the elderly over a decade ago and has been confirmed again by investigators from Mayo Clinic [15]. The defect in fact may reflect an increased susceptibility to sodium-induced calcium excretion.

Calcium has been thought to protect against colorectal cancer, but extensive studies now show no protective effect [16,17]. In contrast, vitamin D intake appears protective.

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Thyroid Hormone and Bone

Thyroid hormone elevates bone turnover, especially resorption [1,2]. There is both bone loss (15% or 1 SD) and increased fracture rates in patients with thyrotoxicosis or those treated with excess thyroid hormone [3,4]. Antithyroid therapy in thyrotoxicosis patients increases both BMD and ultrasound stiffness [5]. Compact bone and total body BMD increased by only 5% over one year, but trabecular sites, including the os calcis, increased by 10% to 15% (Figure 1).

A more subtle problem has been the effect of exogenous thyroxine. Replacement, or even suppressive, thyroxine therapy has little effect on BMD at any skeletal site under normal circumstances [6-14]. Endocrinologists today minimize dose levels in order to reduce side effects on the heart and skeleton [15]. Skeletal effects are greater in postmenopausal women [13,16-19] than in adolescents and younger women, perhaps because the thyroid dose needed decreases with age, but physicians are not decreasing dose enough. Unfortunately many of the studies have been cross-sectional; several longitudinal studies showed accelerated bone loss at daily levothyroxine doses >2µg/kg [14,19-21]. Loss rates are increased by only 50%, which would make the BMD difference between treated patients and controls only ~10% after 5 to 10 years of treatment.

The skeleton of the postmenopausal female is not more sensitive to thyroid hormone [22]. Thyroid excess, like parathyroid hormone, affects compact bone as well as trabecular bone [23]. Cortical thinning and increased porosity decrease bone strength and contribute to increased fracture risk. Postmenopausal women

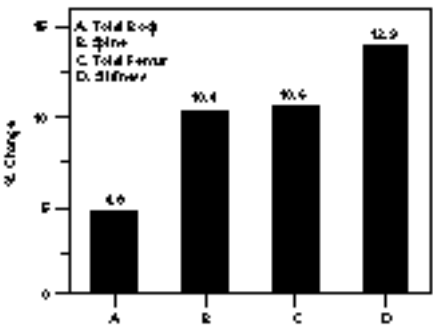

Figure 1. Anti-thyroid therapy for one-year increase BMD and stiffness [5].

with previous hyperthyroidism, or those who have been treated with thyroid hormone, should receive bone densitometry. These patients are potential candidates for estrogen therapy [17,24]. Bisphosphonates could potentially be used to suppress the high bone turnover [25], although calcium alone may be adequate [20].

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ASBMR September 1996

This year's ASBMR in Seattle was the most successful ever in terms of participation, clinical relevance, and sheer exuberance. In fact, many who had participated in congresses of osteoporosis, including the recent one in Amsterdam, agreed that this ASBMR had a much higher level of scientific content and clinical relevance. The meeting was attended by 3600. There were approximately 1600 abstracts and oral presentations, of which about 30% were clinical. As usual, there were satellite symposia on osteoporosis diagnosis, use of biochemical markers, bisphosphonates and calcitonin.

The clinical highlight was on treatment of osteoporosis. The recent introduction of alendronate (Fosamax by Merck) has refocused interest in treatment, at least in the U.S., and rekindled interest in etidronate (Didronel by P&G), which seems to be almost as effective but has less gastrointestinal side effects. Most experts agree, however, that estrogen remains the first line of both prevention and treatment. Reports from the EPIC early intervention trial demonstrated that alendronate had only half the effect of estrogen on the lumbar spine and femoral neck. The most remarkable finding, however, was that alendronate failed to preserve compact bone, while HRT did so. Etidronate also does not preserve compact bone. Since compact bone may be quite important to long-term structural integrity, many physicians interested in prevention will continue to focus on use of hormonal replacement therapy in the immediate postmenopausal decade. For those who do not wish to take estrogen, bisphosphonates and calcitonin are alternatives, particularly in later years. There were few new presentations on calcitonin therapy at the meeting. However, recent reports do suggest that nasal calcitonin (200 IU) can preserve, and in fact increase, lumbar spine BMD.

In the diagnostic forefront, there was virtual unanimity on the need for measurement of axial BMD to ascertain fracture risk. While QCT remains a viable alternative for the spine, DEXA is clearly the preferred modality by practitioners because of its lower dose, accessibility, and routine precision. There was increasing evidence on measurement of femoral BMD, and a recognition that the total hip region, rather than the femoral neck, is both more precise, and more representative. The situation has been complicated, however, by the demonstration that the reference data for the Hologic QDR densitometer are too high by 5% to 10% in both males and females (see "QDR Femur Data," this issue and "QDR Reference Values," July 1996 *LunarNews*). Many leading experts view T-scores with concern because a T-score of -2 or -2.5 for the proximal femur indicates a six- to sevenfold increase of risk of hip fracture. This is not true for measurements of peripheral sites. In order to achieve the same risk, peripheral BMD must be decreased to -4 SD (see "Forearm/Hand BMD," this issue). Researchers from UCSF suggested that it would be preferable to express results in terms of risk of fracture. However, the FDA in the U.S. and other regulatory agencies do not allow any mention of fracture risk in densitometer output, so any such presentation will have to be based on the information provided by professional societies.

Numerous presentations on biochemical markers continued to show that virtually all of these are useful for research on clinical response (see "Biochemical Markers," this issue). Groups of patients with high turnover clearly have decreased BMD, even though such patients do not usually show an increased response to therapy. However, the symposium on markers, and many presentations, showed that the markers could not be used reliably in individual patients for either ascertainment of risk or determination of response. The suggestion that urinary markers could be used clinically is irresponsible.

A common theme regarding secondary hyperparathyroidism seems to be winding its way surreptitiously through the presentations. There appears to be an unusually high prevalence of secondary hyperparathyroidism among the elderly, at least in the northern United States and northern Europe (see "Update: Vitamin D," this issue). This mild secondary hyperparathyroidism is often accompanied by low total body and femur BMD and decreased calcium absorption. In the cases of the institutionalized patients and the home-bound, 25,OH-D levels may be reduced, but in many subjects, the only manifestation is an elevated PTH coupled with a low urinary calcium, indicating a defect in calcium absorption and/or intake. Supplementation with vitamin D can rectify the problem in a large subsegment of this population, however, this is not always possible because there is a defect in renal hydroxilation of vitamin D in the elderly. Many clinicians pointed out the need to correct secondary osteoporosis before providing primary therapy.

Ultrasound densitometry is now well accepted and validated based on a number of presentations, as well as an abundance of recent publications (see "Ultrasound Densitometry," this issue). Prospective studies have now demonstrated that ultrasound of the os calcis indicates risk of hip fracture almost as well as BMD of the proximal femur, and with twice the sensitivity of peripheral BMD. The most remarkable findings, however, have been that ultrasound of the os calcis can be used to monitor therapy. The stiffness response produced by estrogen, alendronate, and calcitonin closely approximate BMD increases seen in the lumbar spine.

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Growth Hormone

It is now obvious that growth hormone (GH) given to children with a deficiency increases height velocity, as well as both muscle and bone mass [1-4]. Early treatment is encouraged because GH deficient adults have a low BMD (-10% or 1SD), increased body fat, and low muscle mass with diminished strength. Compact bone may be particularly affected by deficiency; trabecular bone volume is normal [5]. This bone deficit explains the observations of an increased fracture rate. Therapy with GH increases muscle and bone mass in deficient adult patients [6-8] but the magnitude and speed of the response is less than in children. GH has been shown to have a larger effect in younger animals than in adult animals, and there is a greater effect on compact than trabecular bone [9,10]. Johannsson et al [7] showed a 5% increase in spine and femur BMD, and in total body BMC, in 44 adult patients treated for two years (see Table 1). Studies lasting only 6 to 12 months, however, have shown no change of BMD [11], which led to the view that the GH effect on bone was "disappointing" [12,13]. GH given to normal adults, and to the elderly, also has "disappointing" skeletal effects, but this too may represent the result of short-term studies. Studies lasting 2 or 3 years in the normal elderly have not been done because of side-effects. Long-term studies are not needed to see effects on soft tissue. A few months of GH treatment increases muscle mass and decreases fat [8,14-16], but there is some question about the clinical value of these changes. Does GH cause a retention of water in muscle, or is there an increase in the protein mass?

Table 1. GH treatment of deficient adults (n = 44) for two years increased axial BMD by 4% compared to baseline [7].

	Months	
	12	24
Total Body BMD	100%	100%
L2-L4 Spine BMD	101%	104%
Femur Neck BMD	101%	104%

The potassium content of the fat-free mass in untreated patients does appear low, which may account for decreased strength [17]. Is potassium content and strength actually increased as some claim, or is it not, as others seem to show [15,16]? Myofibrillar protein synthesis is not substantially increased by GH treatment [14]. Clinical trials and clinical use of GH are increasing, and undoubtedly these questions will be addressed by use of DEXA for body composition. Given the costs and uncertainties of treatment, GH may be most useful in those with the greatest bone deficiency or muscle wasting [18,19]. There does not appear to be a positive effect in patients with AIDS [20].

Even short-term GH therapy stimulates bone turnover, and both serum and urinary markers are affected [21-24]. Large increases are observed within the first months of therapy in both deficient and normal subjects. Markers do correlate (r~0.5 to 0.8) with height velocity in treated children. There is little utility, however, of markers in children since height change is much easier and cheaper to measure. In adults there is little effect of GH on BMD until 18 to 24 months of treatment despite an early elevation of turnover; changes of markers in GH treated adults do not correlate with BMD change. Ghiron et al [24] concluded that "even under controlled conditions bone turnover markers exhibit substantial daily variation so that a very large treatment effect will be required for these markers to have clinical utility."

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Peripheral QCT: Better On Compact Bone

Several reports cited in the last two issues of *LunarNews* have shown that QCT of the peripheral skeleton (pQCT) is relatively insensitive to aging bone loss, and lacks diagnostic sensitivity in osteoporotic patients. This has been confirmed again by Grampp et al [1]. The poor performance may be related to large accuracy errors; UCSF researchers reported a predictive error of 15% [2] while Louis et al reported an error of 18% [3]. In contrast, QCT of spinal trabecular bone was useful in assessing age-related bone loss, and provided discrimination of patients with vertebral fractures from controls [1]. The UCSF researchers suggested, as in earlier reports, that the measurement of compact bone was more useful than trabecular bone density. Trabecular bone in the distal radius has low turnover and a structure that differs from axial trabecular bone [4]. Studies over the past decade have suggested that osteoporosis is related to a defect in compact bone more than trabecular bone. Compact bone area declines by about 4% in men and 15% in women with aging [5]. It is possible pQCT could measure the thickness or area of compact bone in the radius shaft [6,7], because this does correlate with strength, not only at that site, but at the femoral neck [7,8]. This cannot be done on the distal radius because the compact bone is much thinner (1 mm) than the resolution of conventional pQCT devices [6-9]. The German pQCT device can be used to measure compact bone on the radius shaft [10]. High resolution pQCT from a Swiss manufacturer appears more capable of measuring the distal region [11,12].

Material density of compact bone in the appendicular skeleton might be particularly important in evaluating susceptibility to fracture and could potentially be used together with measurements of bone density from DEXA to better assess fracture risk. Based on the above studies, pQCT of the distal forearm is an expensive substitute for forearm DEXA, with twice the accuracy error and precision error. Clinicians outside of Germany have been justifiably cautious in use of this approach.

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Biochemical Markers: Adjunct to Densitometry

Research on markers is popular today because the tests are relatively easy to do, and involve minimal patient contact. There have been hundreds of research reports on a dozen different markers, but as yet there is almost no clinical utilization of any of them. There have been several recent reviews of markers [1-4].

Studies continue to show that biochemical markers indicate elevated remodeling in groups of postmenopausal women [5-13], as well as in metabolic bone disease and metastatic disease [14-19]. The new urinary markers (pyridinium crosslinks and telopeptides) are slightly more sensitive than older serum markers (alkaline phosphatase, osteocalcin), but have over twice the day-to-day variability (35% versus 15%). New markers are being developed [20,21], including serum telopeptides which have better precision.

Does the elevated remodeling in postmenopausal women predict bone loss in the individual patient? The results from dozens of studies show conclusively that the correlation of marker levels with change of BMD in either treated or untreated patients, ranges from 0.10 to 0.40 (i.e., under 15% of the variance in BMD is explained by one, or even two markers) [8-13]. Questionnaires predict BMD better than markers. For example, urinary C-telopeptide correlated only -0.1 to -0.3 with BMD at several sites in one major study [8]. In numerous studies over the past several years, investigators found that markers were not predictive of bone loss in untreated postmenopausal women [22,23]. The poor correlations only reflect in part the high variability in markers. Combining two markers, which decreases precision error, makes patient classification more robust [24]; however, it improves the correlation to BMD only slightly. Cosman et al [13] concluded, "We conclude that measuring individual serum and urine markers of bone turnover cannot accurately predict bone loss rates in the spine and hip." An exception may be intact PTH. In a small group of older subjects (>70 years), age correlated as highly with femoral loss as did markers [10], but the predictive value of markers doubled to 40% when PTH was included. PTH is the best single assay for determining skeletal status in subjects over 65 years [25,26]. Serum 25-OH-D is also useful, and like PTH, it correlates with turnover and femoral density [26,27].

If the predictive accuracy of a marker in an individual patient is poor short-term, can it predict BMD long-term? Do women with high turnover and high bone loss at the menopause continue to lose at a high rate? Researchers with a commercial interest in bone densitometry and bone markers claim this. This seems unlikely, since an elevated bone turnover explains only 5 to 20% of the variance in BMD either at the menopause or later in life. Moreover, both turnover and bone loss are not uniformly elevated over time; impartial investigators find that loss rates are normally distributed, and that only 10% show high loss at the menopause and continue to lose rapidly [28]. The variance in BMD does not increase dramatically with aging which would be the inevitable consequence of a persistent difference in loss rates. Body weight at menopause is a better predictor of subsequent BMD than any marker or combination of markers and is much less expensive. Patients who are fast losers average 5 kg lower body weight than the average, while slow losers are 5 kg heavier. Unfortunately prominent osteoporosis researchers are not commercially involved with the manufacture and distribution of scales or this promising technology would be utilized more often.

While studies show that markers do not predict either BMD, or rate of bone loss, they may have a more general usefulness in relation to risk of fracture. High bone turnover is associated with the increased risk of fracture [29-31]. In particular, the high turnover associated with elevated PTH has been found to indicate a risk of hip fracture in the elderly. Can this information be used clinically? A low turnover is no guarantee of a high BMD, and low fracture risk, or vice versa. Patients on corticosteroid therapy have low turnover and a high fracture risk. Moreover, there is a problem of reliable ascertainment given the poor precision of markers. The relative risk of fracture doubles for a 1 SD increase of bone turnover markers. However, the intrapopulation SD of about 35% to 50% for resorption markers is only slightly greater than the precision error of these markers. Thus, one cannot make a reliable determination of risk for an individual patient. Contrast this to BMD (or ultrasound stiffness) where the 1% to 2% precision error is 5X to 10X smaller than the intrapopulation SD of 10% to 20%. When reliable marker tests with a 10% precision are developed, they will prove useful in individual assessment. Until then, experts have concluded that the only method of assessing fracture risk in individual patient is through direct measurement of BMD.

Markers do have potential for monitoring treatment, but for this application, they must have a precision error that is low relative to changes. The elevated marker levels after menopause are usually decreased to normal levels within months by antiresorptive treatments, even those which may have little effect on BMD. For clinical management, however, the individual response, not the average response of groups, needs to be assessed. It is obvious that the variation in urinary markers of resorption is too high to be used for monitoring individual therapy [32-35]. The 30 to 35% day-to-day precision error of these urinary markers is about half the magnitude of the change that occurs from pre-treatment to post-treatment. Given this precision, one could not tell from day-to-day in an individual patient if the treatment was effective. Panteghini and Pagani [34] have characterized the variation and have shown that one needs 59 samples from an individual to define a set point within ±5%; a less rigorous criterion of ±15% requires only 7 samples. Popp-Snijders et al [35] suggested pooling urine samples for a week and then doing one assay to reduce the day-to-day

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variation. Clearly, the best alternative is use of a serum sample which halves the variance of urinary markers. Serum telopeptides have been developed and will probably become available in 1997.

Those wishing to use urinary markers for clinical purposes should definitely read the package insert which indicates they are not to be used diagnostically. Moreover, the label specifies that the urinary markers should be used together with creatinine in order to reduce the usual 30% to 35% variation. Ostex International recently received a warning letter from the FDA with regards to their telopeptide assay indicating the product was misbranded and adulterated. The text of the Osteomark® FDA warning letter is available at the LUNAR internet web site (www.lunarcorp.com).

Markers do not indicate BMD levels, or bone loss. New results show that markers indicate fracture risk despite their poor correlation to BMD. Detailed long-term prospective trials need to be done to show how markers can be used in combination with bone densitometry to enhance assessment of fracture risk. Some markers (those having a precision error of <10%) could become a valuable adjunct to bone densitometry in evaluating the need for therapeutic indication.

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Upcoming Meetings - 1997

Representatives from LUNAR will be attending several of the following meetings. Stop by our booth and see the latest developments in densitometry.

- January 16-19, International Society for Clinical Densitometry, San Diego, California, USA. Contact: International Society for Clinical Densitometry, Phone: 607-336-2663; Fax: 607-336-7489.
- April 16-18, International Meeting on Osteoporosis, Beirut, Lebanon. Contact: Achrafieh/Nasra, Baydoun St., Al Maasarani Bldg., ground floor, Beirut, Lebanon. Phone: +962-1-337-227; Fax: +961-1-337-227/583-599.
- April 26-29, 25th European Symposium on Calcified Tissues, Harrogate, UK. Contact: Janet Crompton - email: 101613.65@compuserve.com; Fax: +49(0)117-924-1208.
- May 15-17, The 2nd International Conference on Steroids and Bone, Siena, Italy. Contact: O.I.C. sr1, Via A. La Marmora, 24, 50121 Florence, Italy. Phone: ++39/55/50.00.631; Fax: ++39/55/50.01.912.
- May 17, Bone Ultrasonometry: A First Symposium for Clinical Practitioners, Scotland. Contact: Healthcare Education Services, Ltd., Apex House, 9 Haddington Place, Edinburgh, Scotland RH7 4AL. Phone: +44-131-557-2477; Fax: +44-131-557-6788.
- May 18-22, 12th International Bone Densitometry Workshop, Crieff, Scotland. Contact: Osteoporosis Research Unit, Victoria Pavilion, Aberdeen Royal Hospitals, Wollmanhall, Aberdeen, AB9 IGS, UK. Fax: +44-1224-404419.
- May 22-24, 3rd International Symposium on Nutritional Aspects of Osteoporosis, Ouchy-Lausanne, Switzerland. Contact: M. Rueger, Dept. of Internal Medicine, University Hospital - CHUV, 1011 Lausanne, Switzerland. Phone: +41-21-3140870; Fax: +41-21-3140871.
- June 4-7, 4th International Symposium on Osteoporosis - Research Advances and Clinical Applications, Washington, D.C. Contact: Kara Mulcahy, NOF, 1150 17th Street, NW, Suite 500, Washington, D.C. 20036. Phone: (202) 223-2226; Fax: (202) 223-2237; E-mail: kara@nof.org.
- June 11-14, Endocrine Society, Minneapolis, Minnesota, USA. Contact: Sherago International, Inc., 11 Penn Plaza, Suite 1003, New York, New York 10001. Phone: (212)643-1750; Fax: (212)643-1758.
- June 20-24, Workshop on Osteobiology - Cell-Matrix Interactions in Health and Disease, Parma, Italy. Contact: Medicina Viva, Servizio Congressi s.r.l., Viale dei Mille, 140, 43100 Parma, Italy. Phone: +39 (521) 290-191/290-194; Fax: +39 (521) 291-314.
- September 4-6, North American Menopause Society, Boston, Massachusetts, USA. Contact: NAMS, Jayne Dalton. Phone: (703) 522-9100; Fax: (703) 524-4672.
- September 10-14, American Society of Bone and Mineral Research (ASBMR), Cincinnati, Ohio, USA. Contact: ASBMR, 1101 Connecticut Avenue, N.W., Suite 700, Washington, D.C. 20036, USA. Phone: (202)857-1161; Fax: (202)223-4579.
- November 13-16, 2nd International Conference on Osteoporosis, Osaka, Japan. Contact: Y. Nishizawa, Office of the Second International Conference on Osteoporosis, Second Department of Internal Medicine, Osaka City University Medical School, 1-5-7, Asahi-machi, Abeno-ku, Osaka 545, Japan. Fax: 81-6-645-2112.
- December 4-6, WHO-IFSSD-EFFO Symposium - Social and Economical Aspects of Osteoporosis, Liege, Belgium, Contact: Advances in Business and Research (A.B.R.), Avenue Rogier 7a, B-4000 Liege, Belgium. Fax: +32-4-221-33-34.

QDR Femur BMD: Misdiagnosis Can Be Corrected

The last issue of the *LunarNews* (July 1996) demonstrated that the reference values for femur BMD provided with the QDR densitometer differed significantly from those observed in the National Health and Nutrition Examination Survey (NHANES) [1]. There is a particular problem with the values for young normal subjects (20 to 39 years) that are used for calculating T-scores. For T-scores to be accurate both the mean and SD for the reference group of young subjects must be correct. The QDR reference values were 7% high at the femur neck, 11% high for Ward's triangle, and 4% high for the trochanter and total regions, compared to NHANES values in U.S. men and women (Table 1 on page 14). The SD values were also low. The net effect is to cause T-scores for all femur regions, particularly neck and Ward's, to be overestimated. The NHANES data on young subjects show T-scores of -0.2 to -0.7 if QDR reference data are used. The DPX reference values closely correspond to the NHANES values after correction for the calibration difference between DPX and QDR densitometers (Figure 1).

Several studies at the ASBMR in September 1996 demonstrated the QDR problem, particularly for the femoral neck. Researchers from Guy's Hospital (London, UK) showed that femur neck BMD in young normal women averaged 0.81 g/cm^2, which is 10% below the QDR reference value [2]. Moreover, the SD in this population was 0.12 g/cm^2, not 0.10 g/cm^2. The observed mean and SD for premenopausal German women (n=100) was 0.81 ± 0.104 g/cm^2 [3]. Premenopausal Spanish women [4] in contrast showed a mean BMD of 0.77 ± 0.12 g/cm^2; however, the women averaged 42 years of age, so the true value for 20- to 30-year-old cases would be ~0.82 g/cm^2. A multi-center European study gave an average BMD before adjustment of 0.84 g/cm^2 for femur neck BMD on QDR densitometers [5]. Femoral neck BMD was closer to the US value in a large group (n=314) of premenopausal Danish women (0.849 g/cm^2) [6]. The average value in premenopausal Australian women was higher, i.e., 0.89 ± 0.12 g/cm^2 [7].

A study reported at the ASBMR [8] examined the prevalence of U.S. women below -2 SD for femur neck BMD. The investigators compared use of NHANES values for young women to the QDR reference values to calculate T-scores. Use of QDR T-scores doubled the prevalence of abnormality (Table 2). The true prevalence in the NHANES study itself was 18% and 33% for women 50 to 59, and 60 to 69 years, respectively. The overestimation of abnormal cases was confirmed indirectly in the Study of Fractures where use of a T-score based on QDR reference values for femur neck BMD

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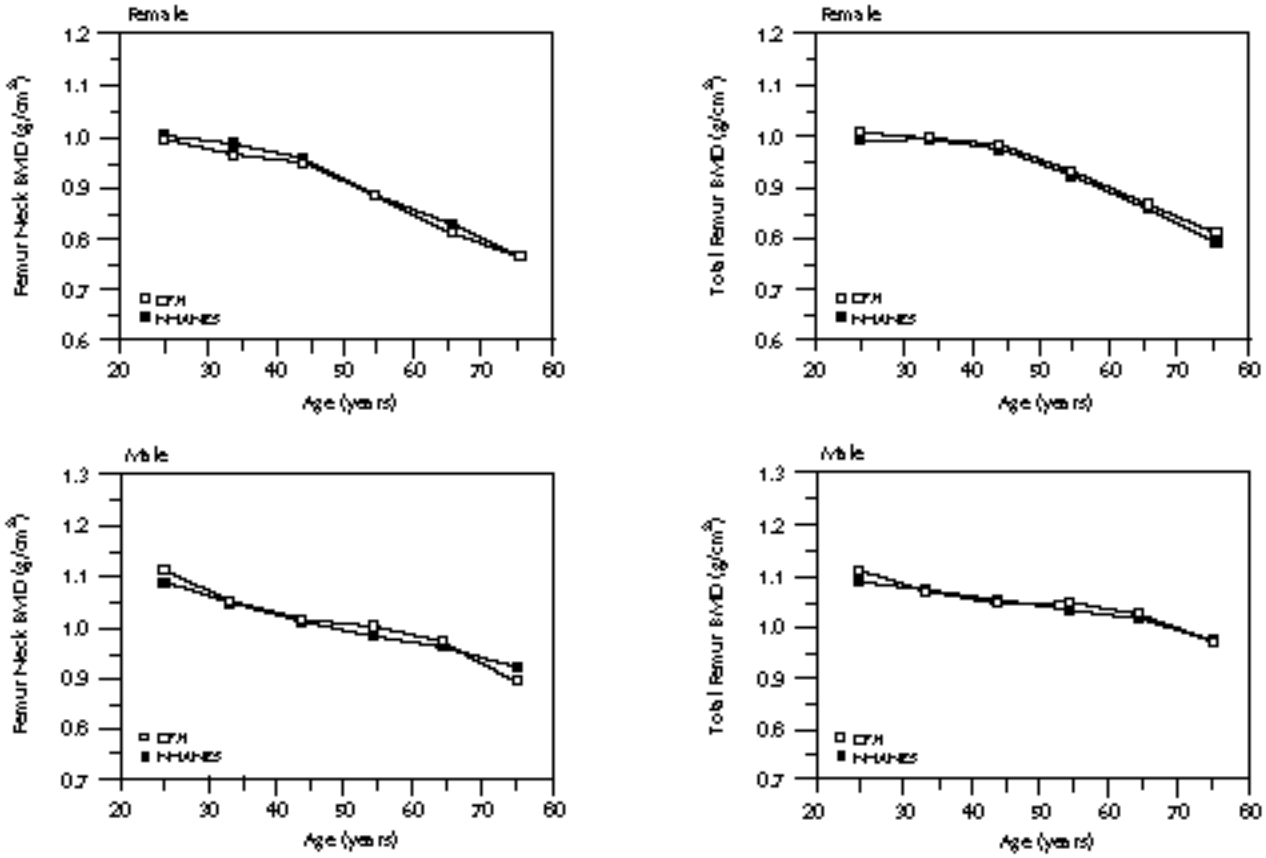

Figure 1. DPX data for femur neck and total femur BMD on 3543 normal women and 454 men compared to NHANES [1]. The latter values were converted to DPX-equivalent BMD.

Table 1. BMD values using the QDR for young normal men and women. The QDR reference values are expressed as a % of NHANES subjects 20 to 39 years data, and T-scores for NHANES were calculated based on QDR reference values.

		QDR Reference BMD (g/cm²)		NHANES [1] BMD (g/cm²)		QDR % NHANES	QDR T-Score for NHANES
		$\bar{x}$	SD	$\bar{x}$	SD		
FEMALES	Neck	0.895	0.10	0.840	0.12	+6.5	-0.55
	Trochanter	0.723	0.09	0.703	0.10	+2.8	-0.22
	Ward's Triangle	0.795	0.11	0.714	0.12	+11.3	-0.74
	Total	0.973	0.12	0.935	0.12	+4.1	-0.32
MALES	Neck	0.982	0.11	0.908	0.14	+8.1	-0.67
	Trochanter	0.800	0.09	0.765	0.12	+4.6	-0.39
	Ward's Triangle	0.832	0.12	0.748	0.15	+11.2	-0.70
	Total	1.071	0.12	1.023	0.14	+4.7	-0.40

produced double the expected number of abnormal cases [9]. A similar phenomenon was observed in a study in Mexico [10].

Table 2. Prevalence of women with femur neck BMD more than -2 SD below young normal using QDR reference data versus NHANES data for young women [8].

Age	n	QDR	NHANES
50-59	229	33%	16%
60-69	60	47%	27%

Why are the QDR reference values for the femur neck so deviant? One explanation could be that the original sample of men and women at the reference data site had extraordinarily high density, or that the particular QDR-1000 used to collect these data was calibrated at the high end of the range. Inexplicable local variations of BMD of ±5% have been observed with both DPX and QDR densitometers [5,11]. If either of these alternatives was the explanation, then the spine BMD from the QDR reference sample also would be incorrect, and BMD for the trochanteric region and the total hip region would be as deviant as the femoral neck; this is not the case. Another explanation may be location of the neck ROI. A shift of the neck ROI from the trochanter to the pelvis changes BMD by about 0.05 g/cm². If the reference data were collected with an unusual neck ROI location, then the reference data would differ from those obtained by QDR users. The analysis guidelines for QDR femur scans emphasize that the superior lateral corner of the ROI touches the interior margin of the trochanter. An additional, and more subtle, reason for the disparity is that Hologic has excluded outlier cases from the data in calculating the reference SD [12]. This means the QDR reference SD for femur neck is 0.10 g/cm² even though the true SD is 0.12 to 0.14 g/cm², depending on region.

Many clinicians have been surprised that the output from QDR densitometers shows a disparity between T-scores for the neck and Ward's triangle versus those for the trochanter and total hip. In 120 older women, Greenspan et al [13] showed the average difference between the T-score for total hip, and femur neck was 0.8 SD using the QDR reference values; it was -1.3 SD for Ward's triangle. There are much smaller differences within the femur when NHANES values are used to calculate T-scores for the data of Greenspan et al (Table 3). For example, the T-score for the femur neck was only 0.2 SD lower than that for the total hip using NHANES reference data. Some users of the QDR densitometer have recognized this as long as five or six years ago, and have in fact subtracted ~0.5 to 1.0 SD from the femur neck T-scores in order to compensate. A few have focused on the total hip BMD which is the least discordant region.

The faulty reference data problem creates great medical, legal, and ethical issues for users of QDR densitometers. Patients could have been misdiagnosed and put on medication unnecessarily. Based on NHANES values, a BMD of -2.5 on the femur neck is actually about -1.7. Many patients who have been

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Table 3. Average BMD (g/cm²) values for femur regions and T-scores in postmenopausal women [13] based on QDR and NHANES. The difference between QDR and NHANES reference data was ~1 SD for the femur neck and Ward's triangle.

	BMD (g/cm²)	QDR T-Score	NHANES T-Score	Δ
Neck	0.638	-2.6	-1.7	0.9
Trochanter	0.570	-1.7	-1.3	0.4
Ward's	0.454	-3.1	-2.2	1.1
Total	0.758	-1.8	-1.5	0.3

diagnosed as osteoporotic on QDR densitometers will be relieved to note that they are not as deviant as initially thought.

The faulty QDR reference data also creates a problem for clinical trials. Many clinical trials have used a criterion of -2, -2.5, or -3 SD at the femur neck for entrance. It was pointed out by Colin Miller two years ago that this criterion was unsatisfactory on QDR densitometers [14]. Several clinical research organizations have reported that sites using QDR densitometers have had much easier recruitment than sites using DPX densitometers. The explanation is now clear, since in fact the criterion being used for entrance was much more liberal. While this is perhaps useful for certain pharmaceutical trials in terms of recruitment, it may ultimately be devastating if regulatory agencies need to review these trials in order to make sure that the trials rigorously adhere to the initial hypothesis on a protocol basis. Many patients already on trial, who have been incorrectly assessed as osteoporotic, may have to be excluded from trials, therefore reducing the power of those trials. In addition, even if those patients are not excluded, frequency of fractures among them will be about half the level anticipated based on epidemiologic models. Consequently, an insufficient number of fractures to demonstrate fracture efficacy may occur. Those trials which have used femur BMD on the QDR devices for entrance would be most susceptible to this difficulty.

Hologic reportedly is in the process of implementing the NHANES values for total femur, and recalling the older values. This is the responsible way of dealing with an embarrassing mistake, and Hologic management is to be congratulated for correcting it after several years of denial. The values for femur neck, which have been used by most clinicians, also need to be corrected. Other regions, such as the lateral spine and forearm, also appear to have erroneously high reference values. QDR users can correct the femur T-scores themselves immediately by implementing the NHANES young normal values in their software. Previous scans then can be reanalyzed. A faster alternative is to use the regression relationships shown below for men and women based on the published NHANES data for whites (Figure 2). A fast empirical approximation is that the actual T-score for femur neck BMD is 2/3 of that indicated with current QDR software. A T-score of -2 is actually -1.3 for women (-1.1 for men); -3 is actually -2.2 for women (-1.8 for men).

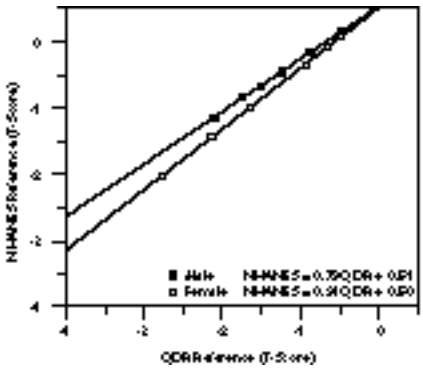

Figure 2. The reported NHANES data by decade for femur neck BMD was analyzed using QDR and NHANES T-scores, and the regression between the T-scores was calculated. The intercept of 0.5 SD represents the overestimation of mean BMD in young subjects for QDR reference, while the slope represents the underestimation of the SD in the QDR reference material.

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Forearm/Hand BMD: Sensitive to Hyperparathyroidism, Not Osteoporosis

Forearm densitometry was introduced commercially 25 years ago based on the development of single-photon absorptiometry (SPA) at the University of Wisconsin. SPA replaced the even older radiographic photodensitometry approach on the hand which had been demonstrated to be unsuccessful for both diagnosis and monitoring. Today x-ray tubes have allowed use of single-energy and dual-energy x-ray absorptiometry (SEXA and DEXA) approaches to peripheral densitometry. The major difference of pDEXA from SPA is speed. SPA required ~3 to 5 minutes to scan at discrete locations on the mid or distal forearm. Today SEXA and DEXA scan the entire distal forearm in this same time frame. Precision *in vivo* remains at ~2%, and the accuracy presumably is comparable to the SPA approach.

Over this 25-year period, hundreds of research studies have shown that forearm and hand BMD have poor diagnostic sensitivity for either spine or hip fracture. The relative risk (RR) for any fracture is only ~1.5 per 1 SD change of forearm BMD [1] compared to an RR of 2.5 of spine BMD for vertebral fracture, or 3.0 of femur BMD for hip fracture. For those clinicians who are confused by RR, another way of comparing sensitivity is the Z-score (difference from age-matched divided by the SD). This is typically only 0.5 SD for peripheral BMD (and for ultrasound of the hand), but ~1.0 for axial BMD (or ultrasound of the heel). Both types of analysis show that axial BMD is at least twice as sensitive as peripheral BMD. Over twice as many osteoporotics with fracture are diminished in axial BMD (>2 or >2.5 SD below young normal) than in peripheral BMD [2,3]. Another way of putting this is that a similar proportion of women over age 60 years will be identified as abnormal using a fixed T-score at different skeletal sites; about 30% using T<-2 SD or 20% using T<-2.5. However, those so identified using axial BMD have 3X to 5X higher risk of eventually fracturing. It is necessary to use a forearm/hand BMD of -4 SD in order to identify patients with equivalent risk of hip fracture to those with a femur BMD below -2.5 SD.

The incremental diagnostic sensitivity of axial sites occurs because there is regional heterogeneity in BMD. Peripheral BMD correlates only moderately (r~0.5 to 0.7) with axial BMD in healthy men and women over age 50 [4-7]. In the EPIC study of postmenopausal women (50 to 60 years), the correlation between forearm or hand BMD with axial (spine/femur) BMD was only 0.5, and the prediction error was ~11% [7]. Even in this narrow well-controlled group, the error in predicting axial BMD was equal to 1 SD in terms of T-score. In patients with bone disease, the correlation drops to ~0.3 to 0.4 [7,8], or about the same as the correlation of BMD with age and body weight. Age and body weight together predict skeletal status almost as well (SEE ~15%) as does forearm/hand BMD [2]. Total body BMD, even though it is not site-specific, is an alternative to spine measurement [5].

Attempts to average BMD from several sites, or to develop composite indices [9], actually decrease sensitivity. This is because inclusion of information from less specific sites inevitably reduces the sensitivity of the most sensitive site, and decreases the positive predictive accuracy.

Patients with forearm fractures have distal forearm BMD 20% lower than age-matched controls, but their spine and femur BMD is only 5% lower. Forearm/hand BMD is particularly useful to assess the risk of forearm fracture [10,11]. The loss rate of forearm BMD in cases with forearm fracture is much lower than controls without fracture [12]. The former group is characterized by either premenopausal forearm bone loss, or rapid postmenopausal forearm loss of short duration. In any event, the osteopenia in patients with forearm fractures is local and is not generalized. The inclusion of patients with forearm fracture in a group of "osteoporotics" biases comparisons between peripheral and axial densitometry, a fact which has been utilized by researchers with commercial involvement in forearm densitometry to demonstrate the "sensitivity" of the forearm. Forearm fracture patients have a propensity for falling [14]; it is this, rather than low axial BMD, that puts them at risk of hip fracture.

Forearm/hand measurements show little or no response to estrogens, bisphosphonates, or calcitonin and hence cannot be used for monitoring therapy. This, together with their poor diagnostic sensitivity, has made densitometry at these sites outmoded.

Forearm/hand densitometry is particularly valuable in relation to both primary and secondary hyperparathyroidism. Patients who have low BMD values in these regions probably should be treated with 800 IU of vitamin D and calcium as a first modality. This is particularly true if they exhibit an elevated PTH. Intact PTH assays today can be done for $15 to $35 and are needed in all elderly patients with low forearm/hand BMD. Those patients who do not respond to calcium and vitamin D may need to be treated with active vitamin D analogs. Those with concomitant axial bone loss can be treated with anti-resorptives. Forearm BMD has been demonstrated to be especially useful in renal patients, and serves better than spine BMD to discriminate those dialysis patients at risk of fracture [14].

Insurance reimbursement for peripheral densitometry has been reduced or eliminated in Japan and Germany in the past year. The Health Care Financing Administration in the U.S. has now indicated that peripheral densitometry will be reimbursed at $37, while axial densitometry will receive $121.

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Forearm/Hand from page 16

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Corticosteroids

Bone loss is almost an inevitable consequence of high corticosteroid levels, either endogenous or exogenous [1,2]. The major effect on bone is depression of formation. A bone deficit of 10 to 20% (~1 SD) compared to matched controls is typical in patients treated chronically with oral steroids. As a consequence the rate of both hip and spine fractures increases by 2X to 6X. A recent study by Peel et al [3] confirmed a high rate of vertebral deformation in treated patients. These investigators suggested, as have several other groups, that the rate of fracture is at least twice that expected for the ~1 SD bone deficit. Others have suggested that the threshold for vertebral fracture may be increased by corticosteroids. If the definition of "osteoporosis" is at -2.5 SD then the threshold could be at -1.5 SD in steroid-treated patients. One possible explanation is the preferential loss of the compact bone surrounding the vertebral body [4].

Corticosteroids are used in a variety of conditions which might themselves have an effect on bone. Rheumatoid arthritis [5,6], inflammatory bowl disease [7], and renal disease [8] are examples. In other conditions such as multiple sclerosis, osteopenia may be a consequence of inactivity rather than corticosteroids [9]. Most corticosteroid problems are associated with relatively low dose oral therapy. There appears to be little bone loss associated with inhaled steroids [10-15]. Almost 2% of postmenopausal women in the UK are on chronic oral corticosteroid treatment (mean dose ≈ 8mg/day of prednisolone) [16], mostly for rheumatoid arthritis (23%), polymyalgia rheumatica (22%) and respiratory ailments (19%). Very few patients (14%) had ever received preventive care for bone loss. Other studies have shown even less attention is given by physicians to skeletal effects.

High-dose steroid treatment is used in transplant patients and is associated with both bone loss and fracture [17-21]. Transplant patients typically develop secondary hyperparathyroidism that requires attention. All patients treated with steroids should receive DEXA evaluation as part of their clinical management.

Management of corticosteroid-induced osteoporosis has been the subject of debate over the past 20 years [4,5,22]. The American College of Rheumatology (ACR) addressed this subject with a consensus statement on treatment [23]. According to the ACR, the treatment should always include calcium and vitamin D (1500 mg and 800 IU daily), as well as estrogen in the postmenopausal woman. Bisphosphonates, calcitonin, and fluoride were suggested for patients who do not respond. Most patients will not respond if only 800 IU of vitamin D is given [24]. In fact, even high doses of ordinary vitamin D may be inadequate. A three-year study by Adachi et al [25] found little long-term effect of 50,000 IU given three times per week with 1000 mg/day of calcium. This regimen tended to inhibit loss for only the first 18 months but did not prevent it. It might be necessary to provide corticosteroid-treated patients with more active forms of vitamin D for long-term success [26]. Fluoride therapy also could be advantageous because it stimulates bone formation and preferentially increases spine BMD. In one study [27] 200 mg/day of monofluorophosphate (26 mgF) increased spine BMD by 4%/year over two years compared to controls. Bisphosphonates and calcitonin can inhibit bone loss induced by low-dose steroids [28,29], but may not inhibit loss due to high-dose steroids [30]. Heart transplant cases are the extreme of the latter group; treatment with 0.5 to 1.0µg/day of alphacalcidol halved

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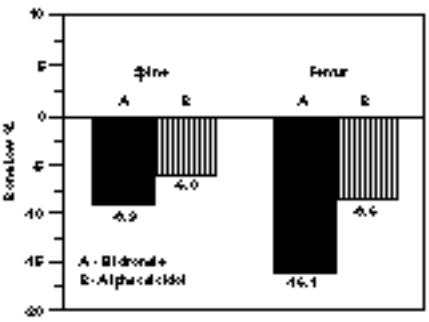

Figure 1. Effect of alphacalcidol on bone loss in heart transplant patients over two years [31].

Corticosteroids from page 17

the high loss seen even in bisphosphonate-treated patients [31]. Testosterone treatment in corticosteroid-treated men increased BMD by 5% in only one year, decreased fat mass, and increased lean tissue mass [32].

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Ultrasound Densitometry: 2% Achilles Precision In Vivo Allows Monitoring

Ultrasound densitometry of the os calcis has been demonstrated to be useful for diagnosis. Numerous retrospective and prospective studies have shown that ultrasonometry, at least that on the os calcis, indicates the risk of spine and hip fracture [1-5]. Retrospective studies have been done with both the UBA 575 (WalkerSonix-Hologic) and the Achilles® (LUNAR) demonstrating that these devices are only slightly below axial DEXA in sensitivity, and well above the sensitivity of peripheral BMD. A major prospective study was published this August. The EPIDOS study in 8000 elderly French women [6], showed that ultrasound using the Achilles was as predictive for hip fracture as femur BMD. Moreover, ultrasound and BMD were somewhat independent so the two could be combined to enhance prediction. This large-scale study demonstrates unequivocally that stiffness, like femur BMD, is several times better than peripheral BMD. A prospective study in the UK on 1800 women (age 45 to 75 years) using the Achilles has confirmed an earlier retrospective study showing that stiffness indicated fracture risk [7,8].

It is not clear why ultrasound measurements of the os calcis, particularly those using BUA, are so diagnostic. Os calcis BMD is generally more sensitive than peripheral densitometry for spine and hip fracture, but unlike ultrasound of the os calcis, it is not comparable in sensitivity to spine and femur BMD. BUA and SOS on the os calcis correlate highly (r=0.8 to 0.9) with BMD at the same site, even though the correlation to spine and femur BMD is only 0.5 to 0.7 [9-12]. Langton et al [11] demonstrated a correlation of 0.94 between BUA and BMD; moreover, BUA predicted bone strength equal to, but not better than, BMD. Ultrasound results depend on the presence of marrow in the bone, but the correlation with BMD is not affected by removal of marrow [9]. Njeh et al [12] showed high correlations (r~0.9) between SOS and elasticity, and suggested that a combination of velocity and density could better predict strength than density alone. Recent studies on dense bovine and porcine bone are not relevant to human bone; they show a dependence of results on bone thickness [13-15]. However, Wu et al [16] and several other groups, have shown there is no significant dependence of BUA or SOS in less dense human bones. The very small dependence that does exist is much smaller than the dependence of os calcis BMD on heel width.

Instruments that measure BUA on the heel should not be confused with those measuring SOS on the hands, tibia, or knee [17-20]. The latter are poorer indicators of fracture risk; the sensitivity on the hand appears similar to that on the knee, but the tibia is much poorer. Results from the US Study of Fractures show that tibia SOS provides a relative risk of only 1.1 per 1 SD change of SOS [21]. Even body weight is several times better as a predictor of fracture risk. Poor results obtained with these SOS devices, like those obtained by ultrasound measurement of skin thickness, have given "ultrasound" a bad name among clinicians who are not well-informed enough to distinguish.

Reproducibility is useful for diagnostic purposes, but it is absolutely essential for monitoring therapy. The most precise ultrasonometry is done using water for coupling. The original research on the Achilles was done using gel-coupling alone, but it was found that the results for BUA were unreliable. That approach was abandoned in favor of using a temperature-controlled waterbath. Moreover, the need to apply, and then clean up, a messy gel was a hindrance. The most common gel-based contact ultrasound is the CUBA (McCue Ultrasonics, UK). This device was based on the considerable acumen of Chris Langton, a leader in ultrasonometry, so it should represent the best results obtainable with a contact device.

Graafmans et al [22] measured precision in 20 patients, 5 times on one day (short-term) and 6 times over 3 months (long-term). The results are given in Table 1. The 5% precision in this study is comparable to that reported by others with both this device and with the WalkerSonix UBA575+ [23-25].

The Achilles differs from other devices by combining BUA and SOS in order to provide significantly better precision than either alone. The precision is better because changes in BUA and SOS due to bone thickness are anti-correlated, so slight positional differences do not affect results for stiffness as much as for its component variables. At least 40 published studies have demonstrated a precision of about 2% *in vivo* for stiffness using the Achilles. In contrast to x-ray absorptiometry, the precision of stiffness is better in osteoporotic women than in young subjects. Precision of the Achilles should be assessed in older subjects as the instrument is optimized to achieve the best results in low density bone.

Until recently, it was thought that the precision of ultrasonometry was not critical because these devices were viewed solely as diagnostic aids. However, recent studies have demonstrated that stiffness changes occurring with the menopause are fairly large (-2%/year) [26]. Moreover, the stiffness increases occurring with therapies are also 1% to 3% annually, and may approximate or even exceed lumbar spine increases. Giorgino presented information showing estrogen increased stiffness by ~4% over 1 year [27]. At the

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Table 1. Comparison of precision in vivo *with a gel-coupling approach compared to Achilles.*

	CUBA [22]		Achilles		
	SOS	BUA	SOS	BUA	Stiffness
Short-term	1.4	3.4	0.3	2.0	1.5
Long-term	1.3	4.9	0.3	2.5	2.0

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ASBMR, these same researchers showed that alendronate increased stiffness by about 3% over two years [28] (see Figure 1). Gionneli et al [29] recently demonstrated similar results with intranasal calcitonin. (see "Update: Calcitonin," this issue). These differences are at least twice the precision error of 2%. Hence, ultrasonometry potentially could be used for monitoring treatment efficacy. Gomez et al [30] showed that thyrotoxic patients had low BMD and low stiffness values (15% or 1 SD below controls). Stiffness and trabecular BMD were normalized by one year of anti-thyroid treatment.

Precision only can be achieved by careful attention to positioning because the heel is highly irregular. Commercial ultrasound densitometers do not provide imaging of the heel at this time, but an image of the heel could be an aid to proper location [31]. However, studies done using heel imaging showed no better precision than with arbitrary placement. Careful foot preparation, use of positioning aids, and restriction of patient movement are the key to precision error.

Changes of urinary markers have been proposed as a possible means for monitoring therapy, but decreases due to antiresorptives are at most twice the precision error of 30% to 35%. Increases in stiffness are usually 2X to 3X greater than the precision error. Moreover, the actual cost of performing ultrasonometry at $10/test is 5X to 10X lower than the costs of a urinary resorption marker, so it may be used much more readily, or frequently, for checking therapeutic results.

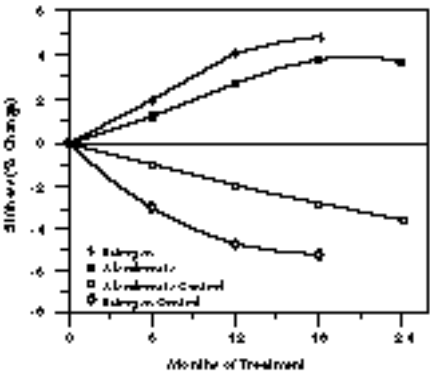

Figure 1. Stiffness changes with estrogen or alendronate treatment [27,28].

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Risk Factors for Osteoporosis: Who Should Receive Densitometry

The development and acceptance of new therapies for osteoporosis is leading health authorities to question who should receive therapy. Low-cost therapy (for example, 800 IU of vitamin D) can be given to all elderly people, but bone densitometry is the "gate-keeper" for high-cost therapy. Directly related to this is the question of who should get densitometry tests, and who should be excluded. The knowledge of risk factors can help in these decisions. For the last 30 years, researchers have identified the risk factors associated with osteoporosis (Table 1). It is obvious now that fractures are most common in white women in regions distant from the equator, and that osteoporosis is rare in blacks [1,2]. Asian women have lower BMD values, but this is largely a consequence of their lower body weight [3,4]. Most of the risk factors associated with fracture are, in fact, factors which adversely influence BMD, but others, such as use of long-acting tranquilizers, compromised visual acuity, neuromuscular impairment, and poor footwear all result in an increased number and severity of falls [5-9]. Leg strength and neuromuscular coordination may be particularly important in relation to hip fracture. Muscle-biopsy in subjects with fresh hip fractures showed a reduction in muscle fiber size [10]. A lower number of falls in Japanese women probably explains the lower rate of hip fracture in this population. Forearm fractures appear to be associated with falls, rather than low axial BMD [11]. Previous forearm fracture is a risk factor for subsequent hip fracture because it reflects propensity to fall rather than femur BMD.

Some factors are clearly protective, such as current use of thiazide diuretics [12] or estrogens, and a body weight over 70 kg in women [13-21]. Only 3% of that subgroup of postmenopausal women weighing >70 kg have osteoporosis. Maintenance of weight may be an index of adequate nutriture and good health, as well as a marker for production of estrone in fat tissue. Certainly, a low body weight (under 55 kg in white women and under 50 kg in Asian women) is associated with low BMD, and increased risk of fracture. Some of the recent studies showing this have been even larger than the U.S. Study of Fractures (n~8000 women) [18]. The study by Gunnes et al [16] involved 30,000 postmenopausal women, while that of Meyer et al [20] involved 6000 fatal hip fractures in 674,000 men and women. Loss of body weight [21] or height [16] with aging is also a strong indicator of fracture risk. Weight alone explains 15% to 30% of the variance in BMD, and percent body fat explains 20% to 40%. Percent fat is substantially better than any index derived from a combination of qualitative risk factors. Soderberg recently reported that a fat mass <13 kg (i.e., ~20% fat) was an excellent indicator of risk in a study of 1300 women [22]. Smoking appears to increase risk of low BMD and fracture in several studies [23-25]. Smoking may operate in part through its influence on lowering body weight and percent fat.

Table 1. Risk factors for low BMD.

Weight <55 kg in women
Weight <70 kg in men
Body fat <20%
Corticosteroids
Thyroid hormone
Low 25(OH)D or high iPTH
Gastrointestinal disease
Liver disease
Renal disease
Anti-convulsants
Alcoholism

In general there are many risk factors for falling, and also a large number for low BMD. Each factor contributes only slightly (<5%) to the risk of fracturing, so it becomes impossible to use these factors individually, or even in groupings, to minimize risks. These risk factors are not specific and do not identify women who should be treated. The single major factor is low body weight, but even this is not very effective [26]. While studies show that classes of people can be identified (for example, the class with high bone turnover or maternal history of fracture), individual members of that class have widely varying risk. A review of the clinical useful of risk factors [27] showed they are not valuable in the individual patient, a result which many others have shown [14-21,28-31]. A group of risk factors can account for only 15% to 30% of the variance in BMD on the average, with 60% to 70% of BMD being determined by genetics and other factors. One recent Merck-sponsored effort (SCORE) claims to account for as much as 40% of the variance in BMD [32], but this approach, even if independently validated, would still be inadequate for "pre-screening." Individual assessment can only be done using bone densitometry, and only done effectively with axial densitometry.

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Densitometry should be done preferentially in older subjects with major indicators: hyperparathyroidism, use of corticosteroids, history of fracture, and low body weight or % fat. There is little rationale to do "pre-screening" with forearm or hand BMD, as the former costs only slightly less than axial DEXA, and the latter cost more. In the typical managed care environment, the annual caseload is 1000 to 2000 patients, and the actual cost (not charge) per axial DEXA scan is under $50 with technician time. The actual acquisition cost of a peripheral X-ray densitometry device, or an ultrasonic instrument, is about $5 per determination assuming a 5-year device lifetime (equivalent to $500/month) and a caseload of 100 patients per month. For similar assumptions, the cost of a DEXA determination is $10 to $20 (based on an amortized cost of $1000 to $2000/month over 5 years) or 2 to 4X more than peripheral densitometers. In both cases, the great majority of the overall cost is for technician and physician time, space needs, and administrative support services (scheduling, billing). There is minimal cost savings derived from using a lower-cost denstiometry instrument since 90% of the actual cost of each determination is not associated with the instrument itself.

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Therapy Update

Actions	Antiresorption	Formation
Cell Effect	Osteoclast	Osteoblast
Bone Effect	Stabilization	Increase
Target	High Turnover	Low Turnover
Agents	Estrogen	Vitamin D
	Calcitonin	Fluoride
	Anti-estrogens	Anabolic Steroids
	Bisphosphonates	PTH

Update: Calcitonin

Calcitonin has now been approved in the United States for treatment of osteoporosis (Miacalcin by Sandoz), and many physicians are using it because of its safety. It has been difficult to show that calcitonin prevents bone loss in the immediate post-menopausal period, but a reduction of bone loss has been demonstrated in older women, and one study showed a reduction of fracture rate. A recent study [1] again showed there was difficulty preventing loss using 200 IU daily in the post-menopausal decade. An intranasal dose of 200 IU three times a week was not effective, but a daily dose was able to maintain both spine and femur BMD. There was not an increase of axial BMD, however, as is evident with both estrogen and bisphosphonates. Calcitonin had a minimal effect (i.e., stabilization) on total body BMD identical to that seen with estrogen, bisphosphonates and vitamin D. Another study by Gonelli et al [2] showed that 200 IU (cyclically for one month on and one month off over two years) increased both spine BMD and stiffness of the os calcis (Achilles) by 2%. In the calcium-treated controls, stiffness declined by 6% while spine BMD decreased by 3% (see Figure 1). This study demonstrates that stiffness may be as good as DEXA for assessing efficacy because it too shows a response. Calcitonin appears to be effective only in the period more than five years after menopause. Calcitonin does not have any adverse effect on crystal composition, bone structure or bone strength [4].

There can be a need for dose adjustment of calcitonin on an individual basis, and biochemical markers could potentially be useful because patient response varies [5]. Multiple samples of markers, perhaps a pooled sample for several days to reduce day-to-day variation, would be useful in making this treatment decision. Alternatively ultrasound stiffness could be measured after 6 to 12 months to determine if the dose was adequate.

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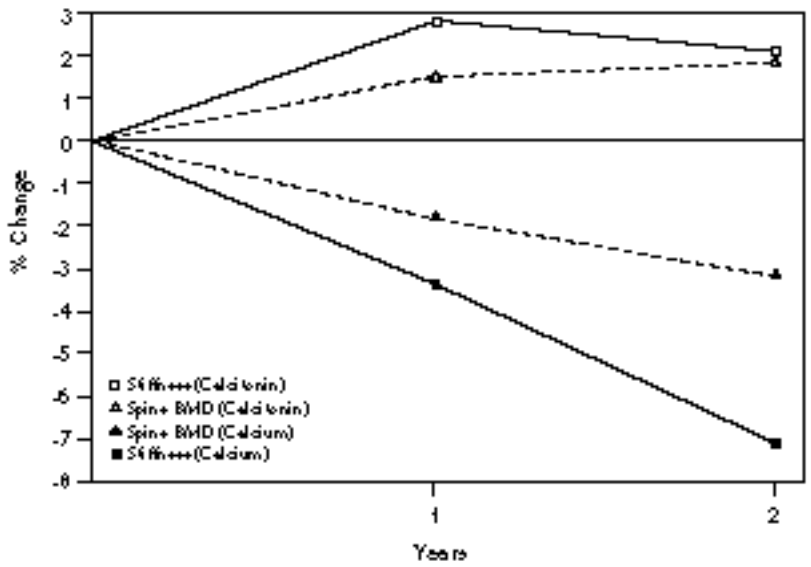

Figure 1. Changes of lumbar spine BMD and stiffness of os calcis over two years [2].

Update: Estrogen

Estrogen has been the favored treatment for osteoporosis in western societies, and it continues to be strongly advocated now that it is available in a single pill for continuous administration (PremPro by Wyeth Ayerst). The launch of PremPro has been one of the most successful in drug history. Estrogen protects against both osteoporosis and cardiovascular disease, but women remain skeptical and/or non-compliant because of side effects, including breast and endometrial cancer [1,2]. There is also a 3X increase in risk of thromboembolism, but the risk is only 1 in 5000 user-years since the prevalence is low [3-5]. Recent studies continue to demonstrate a positive effect of hormone therapy on lipids, and cardiovascular disease [6-11]. A 16-year follow-up in almost 60,000 women from the Nurses Health Study has shown that there was almost no attenuation of cardioprotective effects by addition of a progestin [7]. Progestin is necessary in order to avoid an increased risk of endometrial cancer [12-15]. Progestin can be given at a continuous low dose, or it can be given episodically. Some physicians prefer to provide progestin for 10 to 14 days every 3 months, rather than on a monthly basis, in order to reduce the frequency of periodic bleeding; either this or continuous administration makes long-term estrogen therapy more acceptable.

Estrogen is overwhelmingly the choice of experts for prevention and treatment of osteoporosis because it is both effective and has other positive effects in both peri-menopausal and older patients [16-18]. Spine BMD is increased by 5% to 10% over 2 years, but conventional doses have a lesser effect on femoral BMD [19]. Replacement therapy is especially indicated in younger patients who have ovarian failure, as these patients often have rapid bone loss [20,21]. It also is beneficial in adolescent females treated with thyroxine [22]. Patients who are supplied information on their own BMD values are more likely to initiate therapy and to comply long-term.

The mechanism of skeletal effects, which is mediated by cytokines and growth factors, is under active investigation [23,24]. The bone loss induced by estrogen depletion is associated with high turnover in red marrow, and loss of cancellous bone is slower at sites with yellow marrow and low turnover [25]. Compact bone is also affected, particularly the endocortical region, and intracortical porosity increases [26]. These effects on compact bone, rather than the decrease of cancellous bone, is probably critical for bone strength. Estrogen replacement produces thickening of compact bone and reduction of intracortical porosity [27], in addition to the cancellous hypertrophy seen with antiresorptives. It is the first effect rather than the latter that probably is responsible for the potent anti-fracture efficacy of estrogen. Hormone therapy does not correct structural changes in cancellous bone introduced by the menopause. It preserves existing bone structure but does not reverse structural disruption, again suggesting that cancellous bone and its structure has little role in fracture [28,29]. The use of antiresorptives, such as calcitonin, or bisphosphonates, together with estrogen is probably not very worthwhile in terms of fracture efficacy, although it may produce an increment of BMD in trabecular areas [30]. Calcium and vitamin D (400 IU) should be given together with estrogen [31].

Estrogen therapy is particularly recommended for female post-menopausal patients with mild primary hyperparathyroidism and may be especially useful in preventing the loss of compact bone that occurs in these patients. Experts believe it is a viable alternative to parathyroid surgery [32-35].

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Update: Fluoride

Almost one year ago, it appeared fluoride was assured approval by the FDA, but approval has been slow to come. [1] Studies continue to show that fluoride treatment is effective in increasing BMD. While there are questions about the safety profile, and therapeutic window of ordinary sodium fluoride, both delayed-release fluoride and monofluorophosphate appear to be quite safe. However, there is concern that some individuals could show mineralization defects or other problems affecting bone quality. [2] Unfortunately, the studies that have been done with fluoride have not been on a scale large enough to clearly allay these apprehensions. The safer forms of fluoride probably should be given with 800 IU of Vitamin D to insure adequate mineralization of compact bone [3]. Fluoride therapy may be particularly appropriate for corticosteroid-induced osteoporosis in order to rapidly restore diminished trabecular bone [4-7].

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Update: Anti-Estrogens

Research over the last decade has shown that tamoxifen, a widely used anti-estrogen, prevents axial bone loss, [1,2]. Research has been done on related compounds, [3] of which two are being developed to prevent bone loss: raloxifene (Lilly) and droloxifene (Pfizer). These compounds could be useful inhibitors of bone loss without producing uterine and breast stimulation [4]. Anti-estrogens as a group decrease both bone turnover and bone loss [5-10] and cholesterol [8,9]. Estrogens and anti-estrogens produce stronger bone than alendronate in oophorectomized rats [7]. Tamoxifen patients in clinical trials have had less heart disease than controls [11] so presumably other anti-estrogens could have positive effects. This combination of bone, breast, and heart protective features makes the new anti-estrogens particularly attractive. Experts believe raloxifene will be submitted to the FDA in mid 1997 for approval.

Tamoxifen remains a viable alternative to the newer anti-estrogens. Prophylactic tamoxifen (20 mg/day) was given to healthy postmenopausal women (n=153) in a recent trial [12]. It increased axial BMD by only 1-2%, but decreased cholesterol by 13%. Moreover, tamoxifen could be used together with estrogen to produce incremental changes of BMD and cholesterol [12]. This combined therapy suggests a new approach to treatment if the addition of tamoxifen reduces the elevated (30%) risk of breast cancer due to estrogen therapy. The major difficulty with tamoxifen is endometrial stimulation. This can be effectively controlled by a progestin, which can be administered either once every three months or on a low-dose continuous basis.

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Femur BMD: Should Both Sides Be Measured?

Femur BMD is critical for assessing risk of hip fracture, but measurement of only one femur may not be sufficient. Studies over the past decade [1-6] have shown that there is a high correlation (>0.95) between BMD on the two sides, and that the standard error of estimate is ~0.06 g/cm2 or about 0.5 SD in terms of population variation. These studies show no systematic offset between right and left sides, which has led most investigators to conclude that only one side need be measured. The fact remains that in only two-thirds of the cases is the side difference under 0.5 SD, and in 5% of cases it is expected to exceed 1 SD. A recent study by Njeh et al [6] showed an even higher side difference than expected in 1740 patients. Since risk of hip fracture triples for a 1 SD change of femur BMD, a complete densitometric evaluation requires that both femora be measured. Moreover, care should be taken to match results for side in longitudinal studies.

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Update: Bisphosphonate

The FDA approval of alendronate (Fosamax by Merck) a year ago has stimulated interest of clinicians around the world in use of bisphosphonates for treatment of osteoporosis [1-3]. Alendronate has now been approved in 46 countries, while sodium etidronate, a first-generation bisphosphonate (Didronel by P&G which has been widely used for Paget's disease and hypercalcemia of malignancy for 20 years) has been approved for treatment of osteoporosis in many countries, although not in the important U.S. market. The longest clinical experience has been achieved with etidronate; etidronate continues to have a positive effect in osteoporosis clinically for seven years without any negative effects on mineralization [4-6]. Alendronate has a greater skeletal effect at lower doses [7], but otherwise has similar characteristics to etidronate. Both bisphosphonates preferentially affect trabecular bone, particularly the lumbar spine where BMD increases of 5% to 10% occur over the first two years of treatment. The response of the proximal femur is about half this magnitude. There is virtually no response of peripheral BMD, and in fact, recent studies with alendronate have confirmed the long-observed fact that compact bone, for example, radius BMD, decreases with bisphosphonate treatment. Over a decade ago, Jan Dequeker (Belgium), a leading rheumatologist, indicated that bisphosphonates was not the first treatment choice in patients with low compact bone. Bisphosphonates should be used preferentially in patients with low spine BMD, not those with low radius BMD. The latter group represents, in part, patients with primary and secondary hyperparathyroidism. Despite the negligible effect on compact bone, and on total body BMD, bisphosphonates produce about a 50% reduction in the rate of vertebral fractures [8], apparently due to the strong effect on trabecular bone. Bisphosphonates now have been proven effective, and they do not cause mineralization defects at low doses, but what about side effects?

The patient, a physician, had taken the medication as usual, with a full glass of water upon waking in the morning. Dr. X then proceeded to dress and go directly to the office without eating. Thirty minutes later, Dr. X experienced chest pains, with gastric upset, and one-hour later was in a hospital emergency room. Endoscopy showed perforation of the esophagus with profuse internal bleeding. Is this a bisphosphonate horror story? Not really—the medication was 175 mg of aspirin. At the American Society of Gastroenterology meeting this October in Seattle, clinical investigators reported that alendronate, like aspirin, could be a potent irritant to the esophagus and gastrointestinal tract. The influence, if any, on *Helicobacter pylori* infestation, ulcers, and adenocarcinoma is unknown.

At recent meetings, like the American Society for Bone and Mineral Research and the American College of Rheumatology, many U.S. and European prescribers informally discussed the incidence of alendronate side effects (10% to 20%) which were higher than those expected. One explanation is that side-effects from any drug are common in the elderly, and another explanation is that physicians may be treating patients with a history of reflux or gastritis. A report published in the *New England Journal of Medicine* [9] attracted attention to the problem, and suggested that half or more of the gastroesophogeal problem could be minimized by proper administration [10]. Alendronate must be taken upon awakening with a full glass of water, and the patient cannot recline. While some physicians claimed the side effects were not due to poor administration, the number of reported adverse incidents per patient has dropped since Merck sent out a letter to physicians. A total of 200 incidents had been reported to the FDA as of September 1996, of which only 20% were serious. There may be some underreporting of mild incidents because affected patients terminate treatment, but not of serious side-effects, which are rare. Experts still view alendronate positively, but etidronate may be preferred in the most elderly patients since its side effects are lower. All bisphosphonates can cause stomach upset, cramps, and diarrhea, but amino-bisphosphonates (pamidronate and alendronate) have a higher potential for inducing esophagitis and ulceration. Pamidronate, which is effective in preventing trabecular resorption [9], has been limited to intravenous administration. Side effects should not postpone the FDA approval of alendronate for a prevention indication in the U.S., an approval which is anticipated early in 1997 based on positive efficacy data. Preventive intervention is given to women age 50-65 years, a group in which the frequency of gastroesophogeal side-effects is low. The EPIC study, which was reported at the ASBMR [12,13] showed that low-dose (5 mg/day) alendronate over two years increased axial BMD (spine 3.5%, femur 1.8%) in early postmenopausal women (Figure 1). The magnitude of the response was about half that achieved with estrogen at the spine and femur, but unlike estrogen, alendronate did not prevent loss of radius BMD, even at the trabecular ultradistal forearm site. Estrogen produced a 2X to 4X greater increase in total body BMD and maintained radius BMD.

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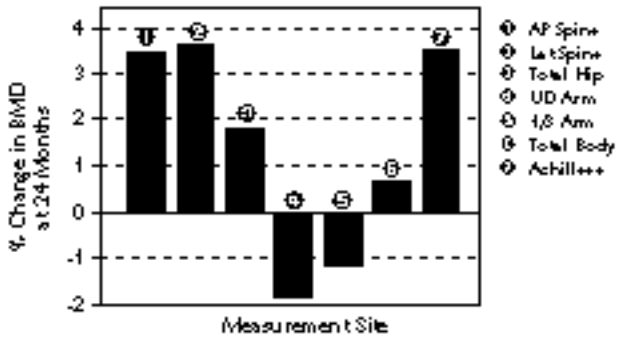

Figure 1. Response at different skeletal sites to 5 mg/day of alendronate in postmenopausal women [11]; Achilles results from Giorgino et al [12].

Bisphosphonate from page 27

However, not all peripheral sites are unresponsive to bisphosphonates; stiffness of the trabecular os calcis increased by 4% over two-years with alendronate [14].

Clinicians in the U.K., Canada, Australia and Sweden, where there has been extensive experience with etidronate, seem to prefer this agent because of its lower cost, (one-third to one-fourth that of alendronate), and lower incidence of esophageal and gastrointestinal side effects. Etidronate is given cyclically (2 weeks out of a 12-week period), rather than on a daily basis, so the frequency of side effects would be much reduced, even if the side effect profile was identical on a daily basis. Etidronate is also given cyclically to treat corticosteroid [15,16] and GnRH-induced bone loss [17]. Clodronate is a bisphosphonate that can be given orally and increases spine BMD [18,19]; it has even less side-effects than etidronate. Intravenous clodronate increased spine BMD by 6% over 6 years and decreased vertebral fracture rate [20]. Cyclic low-dose risedronate is another alternative. This agent is effective in osteoporosis including that due to corticosteroids [21]. Bisphosphonates must be given for years as discontinuation leads to rapid bone loss [22,23].

Monitoring of bone response to alendronate is not needed at frequent intervals because all subjects who take the drug reduce bone resorption within months, and >90% reportedly increase spine BMD. Bisphosphonates with a smaller effect on bone can be evaluated at an annual interval [23].

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Update: Vitamin D

Vitamin D continues to be rarely used as a treatment for osteoporosis in North America and Europe, although it is widely used in Australia and Asia. This is unusual in view of the well-documented calcium absorptive defects and elevated PTH in the elderly, particularly in patients with osteoporotic fracture [1]. Secondary hyperparathyroidism is common after age 65 in northern zones, at least seasonally when sun exposure is low [2-5]. A low 25-OH-D level is more characteristic than low 1,25-D_3. PTH levels increase with aging; low 25-OH-D and elevated PTH correlate directly (r=0.4 to 0.8) with the decrease of total body and femur BMD [6-9]. Secondary hyperparathyroidism is a common metabolic disorder in patients with low BMD values [10], and is the primary defect in hip fracture [11].

Treatment or normal elderly subjects with low doses of vitamin D_2 or D_3 (400 IU) increases serum levels in a few months and lowers PTH [12,13], but may not suppress resorption. Treatment with modest doses (800 to 1000 IU) is sufficient to normalize the elevated resorption markers to the levels of young people within a few months [14,15]. This safe "anti-resorptive" therapy is just as effective as estrogen or potent bisphosphonates in the elderly. If every person over 60 years of age received two conventional multi-vitamins (containing 800 IU per day), the rate of hip fracture would be reduced by 37% to 55% [16] at a cost of only $25 per patient-year. Another alternative is the annual, or seasonal, treatment with a single injection of a "mega-dose" of vitamin D [17].

Treatment of elderly French women with only 800 IU of vitamin D increased femoral BMD and decreased the rate of hip fracture [18]. A similar effect was not seen in Dutch women treated with only 400 IU [13]. Not all of the elderly can be treated effectively with ordinary vitamin D, due to the common defect in converting vitamin D to active hormonal forms. This is particularly true in patients with established osteoporosis, who also have defects of calcium absorption and PTH suppressability associated with end-organ resistance to vitamin D. Parathyroid resistance coincides with gut resistance, which probably explains why osteoporotic patients have an absorptive defect that is not the primary cause of their secondary hyperparathyroidism. As a consequence, treatment with alphacalcidol and calcitriol may be necessary [19]. These agents are stimulators of osteoblastic function [20]; they not only suppress PTH, and decrease bone resorption [21-24] but produce better mineralization and decreased porosity of compact bone. However, they do not increase trabecular density like antiresorptive therapies, so their effects are more difficult to ascertain. Estrogen therapy in patients with osteoporosis is useful, but vitamin D co-therapy must be given [24].

Treatment with active forms of vitamin D has a profound effect on fracture, even though BMD is not increased by more than a few percent. In one recent study, fracture rate was decreased by 70% by only 0.5 to 0.75 µg/day of alphacalcidol. This occurred with this modest dose of active analog even though total body BMD was maintained, not increased (as is the case with potent anti-resorptives), and spine BMD increased by only a few percent [25,26]. Alphacalcidol was equally effective in the immediate postmenopausal (55 years) as in older (71 years) osteoporotic women. In another study, treatment with 1 µg/day of calcitriol increased spine and total body BMD by 1%, but it halved the fracture rate, and the decrease of spinal height [27,28] (see Figure 1). Variability in response to active vitamin D analogs may relate not only to initial calcium absorptive status and degree of secondary hyperparathyroidism, but on vitamin D receptors [29,30].

Vitamin D treatment is useful for the secondary hyperparathyroidism occurring post-transplantation [31] and after corticosteroids [32,33]. Material density of compact bone appears to be where these active vitamin D agents have their greatest effect.

Vitamin D also may have beneficial effects in reducing the frequency of colorectal cancer [34,35], as well as other cancers. Recent reports suggest that higher levels also protect against osteoarthritis.

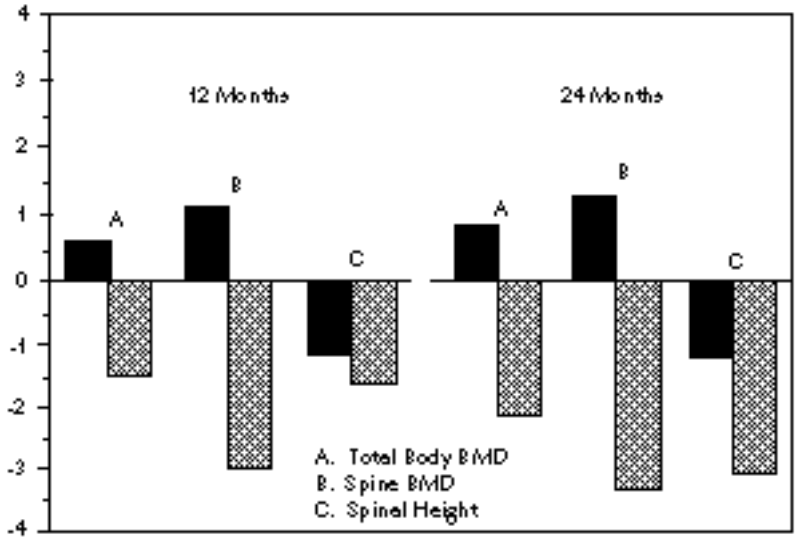

Figure 1. Percent changes after 12 and 24 months in osteoporotic women treated with 1 µg/day of calcitriol (n = 35) or 1000 mg/day calcium (n = 45) [28]. Shaded areas for calcitriol patients. All changes significant at p<.005.

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On behalf of the entire LUNAR staff, I would like to wish all of our customers and friends a stellar holiday season and a happy new year. We look forward to serving you in the coming year.

Richard B. Mazess, Ph.D.
President

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