LUNAR® NEWS

Spring 1999

FROM THE LEADER IN BONE MEASUREMENT

New: PRODIGY™ for Totally Automated Densitometry

The new **PRODIGY** densitometer is the world's most advanced DEXA densitometer. It provides excellent precision, low dose, fast speed, and high spatial resolution. The narrow-angle fan-beam uses a novel array detector made of **Cadmium Zinc Telluride (CZT)**. CZT provides direct conversion of radiation into electrical signals and is energy-sensitive. The high efficiency of CZT translates into 10X lower dose than conventional array detectors using photodiodes. **This higher efficiency is used to reduce scan time to 30 seconds for spine and femur exams and under 5 minutes for total body exams.** The faster speed does not compromise routine precision of 1% with outstanding images.

The exclusive SmartScan™ software also facilitates throughput. **Sophisticated algorithms are used to automatically position regional scans—no time-wasting scout scans are needed!** The bone edges are monitored during acquisition, and the scan path adjusted to center the bone within the field—rescans due to improper positioning are not needed.

A new, user-friendly software interface in WindowsNT® is provided with PRODIGY. The icon-driven interface, designed for even the computer novice, guides the operator through all acquisition and analysis procedures. An on-screen Help program readily answers questions. **PRODIGY's automatic analysis provides patient results with one keystroke—little or no operator intervention is needed**. This also greatly simplifies training, and facilitates use of PRODIGY in larger departments where many technicians will have responsibility.

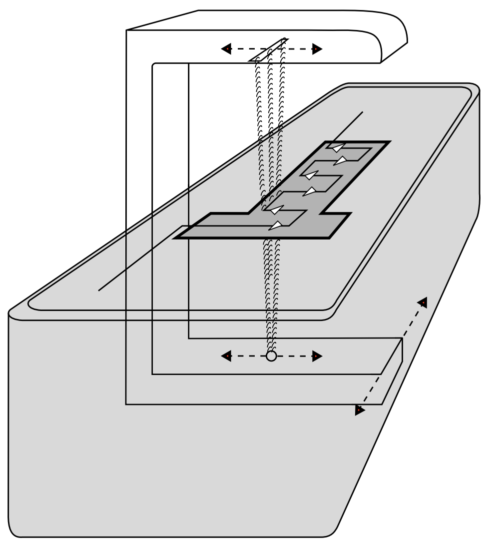

Figure 1. **PRODIGY** uses a narrow-angle fan-beam that is oriented longitudinally and moves laterally, seeking out and scanning only specified regions.

Spine and femur BMD values are identical using the DPX® and PRODIGY (Table 1). Also, results from total body scans (BMC, BMD, lean tissue, and fat tissue) are identical. This allows the PRODIGY to use existing reference data collected with the DPX and EXPERT™ densitometers.

*Table 1. BMD results were obtained on 50 subjects using the DPX-L™ and **PRODIGY** densitometers. The results were essentially identical.*

SITE	r	REGRESSION	Mean BMD (g/cm^2) DPX-L	Mean BMD (g/cm^2) PRODIGY
Femur (Total)	0.99	Y = 1.00X - 0.001	1.001	0.990
Spine (L2-L4)	0.98	Y = 1.00X + 0.005	1.183	1.181
Total Body	0.98	Y = 0.99X + 0.013	1.185	1.182

In This Issue

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NOF Guidelines: Widen Diagnostic and Treatment Recommendations

The long-awaited Physician's Guide to Osteoporosis from the National Osteoporosis Foundation (NOF) recently appeared after an extensive period of evaluation. The Guide was developed in collaboration with, and is endorsed by, several interested societies including the ASBMR, the Am. Association of Clinical Endocrinologists, Am. Acad. Orthopedic Surgeons, and the American Colleges of Rheumatology, Radiology, and Obstetrics and Gynecology.

The guidelines call for wide use of bone densitometry, particularly of the femur. Results for femur neck BMD formed the basis of the theoretical evaluation, thus the T-scores used in the NOF guidelines should be considered relevant to that site. Skeletal sites with lower diagnostic sensitivity for hip fracture, and less response to therapy, are not as clinically useful. **Bone densitometry is recommended for all women over 65 years, and additionally for postmenopausal women with a fracture or with one or more risk factors for osteoporosis**. In the past, recommendations for densitometry have focused on women with several risk factors, of which fracture was paramount, but have stopped short of recommending measurement at any age absent risk factors [1-7].

The NOF recommends treatment intervention at a femur T-score of -2.0 if the patient has no other risk factors, and at -1.5 in the presence of other risk factors. These values represent a considerable "liberalization" since many experts believe that intervention is not justified unless the T-score is at least 0.5 SD lower, i.e., -2.0 with risk factors, and -2.5 or even -3.0 SD without risk factors (corresponding to a Z-score of about -1). The latter, more conservative figures are supported by studies which show that **treatment with high-cost drugs is not cost-effective except when targeted to patients with the highest risk [8-10]**. The limitation occurs because of the large number of patients that need to be treated in order to prevent clinical fractures. In the FIT study of patients with low femur BMD (below -1.6 SD) and prevalent fractures, alendronate halved the risk of fracture during the trial [11]. Still, this reduced the hip fracture rate from 2% to 1%; in other words, it required almost 300 patient years of treatment to stop one hip fracture. The cost per patient-year of treatment with current therapies is $500 to $1000, so the cost in such high-risk patients for reducing fracture is $150,000 to $300,000. By increasing the T-score by 0.5 SD (from -2.5 to -2.0 SD), twice as many postmenopausal patients will have to be treated to stop each fracture.

The recent results from the FIT trial in patients without prevalent fracture showed that alendronate treatment for four years decreased the overall rate of clinical fracture by 14% [12]. **A more positive finding was that alendronate produced significant fracture reduction (36%) in that subset of patients with a femur neck T-score below -2.5 SD.** From both a cost-effectiveness and a therapeutic efficacy viewpoint, many experts, therefore, believe a much lower T-score (about -3 SD) for intervention is warranted. On the other hand, patient advocacy groups wanted to have a higher T-score threshold in order to allow therapy to be given to a much wider group of patients. The NOF guidelines on intervention represent a compromise between health-economics and patient-advocacy, but one that may run into opposition now that anti-resorptive therapy in high BMD groups appears less effective than assumed. **Several regulatory bodies have already determined that treatment of osteoporosis should be allowed only when patients have a history of fracture or a femur BMD below -2.5 or -3.0 SD**. In the future, health management groups, as well as regulatory agencies, are likely to take a more stringent view with regard to drug intervention.

Single copies of the Physician's Guide are available from the NOF (Fax 202-223-2237). Packs of 10 are available for $15. A simpler Pocket Guide, suitable for distribution to primary care physicians and patients, is available in packs of 10 for $5. Physicians better understand densitometry, and refer more, when provided with explanations [13]. Patients better understand their risk when informed directly of their densitometry results, and the Pocket Guide could further help patients' understanding [14].

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Fracture Risk: Tempest on T-Scores

T-scores normalize bone mineral density (BMD) values by using the standard deviation (SD) in a young normal population as a common denominator [1]. There has been heated debate for the last five years since a select committee of the WHO suggested use of T-scores for BMD as an indication of fracture risk [2]. Those guidelines characterized a T-score of -1 as indicating low bone density or *osteopenia*, while a T-score of -2.5 SD was characterized as *osteoporosis*. A patient with a T-score of -2.5 and a fracture was considered to have *severe osteoporosis*. No specific guidelines were given for treatment, but many experts feel that expensive therapy (>$300/year) should be restricted to the latter group of patients who have the highest risk of future fracture. **About 30% of all postmenopausal women are below -2.5 SD at the spine, femur, or forearm, but only about half that number (15%) are osteoporotic at the femur neck [3]**. Under 10% have low femur neck BMD coupled with an osteoporotic fracture; this is the group that shows the greatest responsiveness to therapy (see Bisphosphonates, this issue). In contrast, pharmaceutical companies have advocated treating a much broader group (about 70% of postmenopausal women) with osteopenia or osteoporosis. The initial WHO guidelines were based on forearm measurements and defined the lowest quintile of the postmenopausal population, a group which has a 30% lifetime fracture risk. **However, forearm BMD is rarely used today, except in Japan, because of its diagnostic limitations in women under age 70, and its inability to show response to therapy**. As a consequence, T-scores have been used for the spine, proximal femur, finger, and os calcis.

There has been some concern that T-scores add a new dimension of uncertainty to diagnosis because there is (a) difficulty in accurately characterizing the SD in young adults, (b) uncertainty in what age group (20 to 29, 20 to 39, 20 to 49) is young adult, (c) a small uncertainty in the mean value of a young adult population, as well as (d) precision errors in the patient value [4].

Several reports at the recent ASBMR/IBMS in San Francisco (December 1998) focused on the differences of T-score at different skeletal sites and the lack of concordance among them [5-8]. Some of the differences in T-scores may be due to database deficiencies, such as the well-known error in QDR femur values [1] . **However, differences in T-scores among different skeletal sites today do not appear due to such deficiencies, but rather to much different rates of aging bone loss among sites.** For example, trochanteric BMD decreases only slightly with age (10%), so the T-score at that site is only -0.8 in 65-year-old women [6]. In contrast, the T-score for Ward's triangle is 2 SD lower (-2.8 SD). These disparities were pointed out by Faulkner et al [5]. Why should over half of postmenopausal women be "osteoporotic" at the Wards triangle, yet 90% of the same women are "normal" at the trochanter? Not only have **T-score differences at the same site engendered confusion, but there are also differences among sites**. Os calcis BMD declines with age a bit more than trochanteric BMD, but the SD of the former is larger so that the T-score reduction with age is similar.

The National Osteoporosis Risk Assessment (NORA) project on over 30,000 women has demonstrated that only 8% of postmenopausal women were below -2.5 SD using forearm BMD rather than the 17% that are below that level using femur neck BMD [9,10]. Using heel BMD (with the Osteoanalyzer™) only 2% of white women under age 70 had a T-score below -2.5 SD. This differs dramatically from results for Stiffness of the os calcis using the Achilles+™ (see Ultrasonometry, this issue). At the ASBMR, French investigators [11] reported that Stiffness showed about half of older (>75 years) participants in the EPIDOS study were below -2.5 SD, as did femur neck BMD (52% and 48%, respectively). About 75% of the subjects with femur fractures had femur BMD <-2.5 SD; 75% of fracture cases also had Stiffness <-2.5 SD.

New approaches need to be taken to evaluate fracture risk that better compensate for variable aging changes of BMD. One possible approach defines abnormality by identifying the lowest centiles of the aged population (i.e., lowest 15 and 30), or by using Z-scores. **Treatment could be restricted to patients at least 1 SD below age-matched controls.**

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Bone Biomechanics: Direct Relevance to Fracture *In Vivo* Unclear

Over the past 20 years there has been an ever-increasing number of biomechanical studies that examine the strength of the spine and femur. **The most recent studies confirm what we have known for over a decade: there is a very high correlation (r~0.9) between strength and bone mass or density [1-5]**. A high correlation has even been shown in mice as well as man [6]. One interesting finding is that the correlation with strength decreases when the DEXA measurements are made with soft tissue present. This obviously reflects the greater accuracy error in measuring BMD due to soft-tissue. German researchers [7,8] examined the relation between DEXA results and femoral strength in 58 cadavers; the correlations between BMC and failure load decreased from the usual 0.9 level to 0.6 to 0.7. These results suggest that better fracture prediction could be achieved if DEXA were made more accurate; there is currently an accuracy error of ±3% on excised bones, but this increases to about 8% when soft-tissue is present. Better compensation for variable soft-tissue in femur densitometry could potentially provide even better indication of strength and presumably fracture risk. Stiffness of the os calcis, which can be readily measured with little influence of soft-tissue (at least with non-contact ultrasonometers), predicts femoral and vertebral strength as well as axial BMD [7] (see Ultrasonometry, this issue).

Another reason that ultrasonometry may prove surprisingly diagnostic is because **the combination of BUA and SOS is not only more highly correlated to bone strength than either variable alone, but than BMD itself [9,10]**. SOS in particular seems to reflect bone structure, and correlates well with Euler number, a measure of trabecular connectivity [11]. However, this structural variable may not contribute greatly to strength [12].

There have been continued attempts to do more detailed analyses (curved beam, fractal, finite element) of axial bone [3,13-17]. These have been largely academic exercises in the past, with little obvious relation to clinical reality, but the newer studies are examining the models in relation to osteoporosis. One difficulty has been that such studies can show different and, at times, contrary results. Even slight differences in model cause dramatic differences in results and interpretation [17]. Another difficulty has been that biomechanical studies usually show that bone strength changes proportionally to bone mass, i.e., a 20% decrease in mass decreases failure load by 20%, or in some studies even less. In contrast, a 20% bone decrease increases fracture rates by 300 to 400%, i.e., **the effect of bone mass on fracture risk is at least ten times greater than its effect on strength**. This suggests that both bone densitometry and biomechanical measures are only <u>indirect</u> indicators of the specific anatomical defects that lead to fracture. **Some of the most exciting work on femoral fracture has come from Cambridge (UK) researchers [18,19] who found that porosity of the compact bone in the femoral neck may be a major anatomical determinant of fracture.** Mineralization of compact bone also may contribute to fracture resistance [20] and could help explain why bisphosphonates prevent fracture even though they do not increase trabecular bone volume.

One of the most overlooked aspects of "biomechanics" is the finding that bigger bones tend to be stronger than smaller ones and show fewer fractures. Mazess et al [21] and Gilsanz et al [22] showed that vertebral size was smaller in women with osteoporotic fracture. In the former study, the projected area of L2-L4 was 11% lower in 327 women with vertebral fracture than in 657 controls (Table 1) [21]. In Gilsanz et al [22] the cross-sectional area of vertebral bodies was 8% lower in fracture cases. Vega et al [23] have shown that men with vertebral fractures have 15% lower area (Table 1). **As a consequence of the smaller area and lower density, the bone mass was 30 to 40% lower in fracture cases than controls**. Femoral area also is important in strength and fracture resistance [24]. **The misguided attempt to normalize BMD by calculating an estimated "volumetric density" actually disguises this difference and decreases diagnostic sensitivity.**

Table 1. Area (cm^2) of L2-L4 spine in male and female osteoporotics versus controls.

	Men [23]	Women [21]
Control	53.7	41.7
Fracture	45.7	37.1
Δ (cm^2)	8.0	3.6
Δ (%)	85.1	89.0

The structure of trabecular bone undoubtedly contributes to bone strength, and numerous studies have suggested that non-invasive assessments of texture, from radiographs or MRI, differed in osteoporotic and normal cases. The heel is readily accessible and high-resolution devices, like the PIXI®, may be suitable for structural analysis. New studies using texture analysis of the calcaneus showed significant differences between osteoporotics and controls [25-27].

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Year 2000 Compliance on LUNAR Instruments

LUNAR's complete line of densitometry, MRI, and C-Arm products is currently designed to maintain Year 2000 compliance by correctly reflecting dates following the turn of the century. LUNAR software will correctly reflect dates and patient ages, regardless of whether the data were acquired prior to or after the year 2000. LUNAR systems installed prior to December 1997 may not have the latest software version and thus not be Year 2000 compliant. Refer to the table below to verify that your system is equipped with the most current software. If you are not using one of the software versions shown, you will need to update your system to become year 2000 compliant. Without this upgrade, your system may not correctly reflect dates and patient ages when using the system after the year 2000. Software updates (FDA Code SU) are offered at no charge. Note: Computers must be a 486 or better to run LUNAR's Year 2000 compliant software.

Year 2000 Compliant Software Versions:			
Product	**Software Version**	**Shipped on New Systems After**	**Year 2000 Update Availability**
ACHILLES®	1.5N	N/A	Summer 1998
ACHILLES+	all versions	–	all systems
ARTOSCAN®	all versions	all systems	–
DPX (L, αlpha, +, A)	3.65	December 12, 1997	Spring 1998
DPX-IQ®, DPX-MD™	4.3	July 18, 1997	Spring 1998
EXPERT	1.72	February 23, 1998	Spring 1998
ORCA®	all versions	all systems	–
PIXI	all versions	all systems	–
PRODIGY	all versions	all systems	–

Bone Loss in Men

Bone changes with aging in men have not been investigated as closely as those in women, but there still have been substantial advances over the past 20 years [1-3]. Bone loss does occur in older men, and in fact, **loss of purely trabecular bone occurs at almost identical rates in the two sexes [4]**. Trabecular density of the spine by QCT decreases dramatically in men, but BMD by DEXA is constant (reflecting the stability of spinal compact bone in men without fracture). **In males, about 13% of older subjects have BMD values below -2.5 SD for femur, spine, and forearm, compared to about 41% for females [5] (see Table 1); this is directly comparable to the lifetime risk of fracture in the two sexes**. In men, as in women, the femur neck was the most sensitive femoral site; the trochanter dramatically underestimated risk, as did the total femur. Use of the forearm site doubled the number of abnormal cases in both men and women.

Table 1. Prevalence (%) of subjects below -2.5 SD; adapted from Melton et al [5]. The reference values for young adults were taken to be 20 to 49 for men, and all premenopausal women.

SITE	MEN	WOMEN
Total Femur	3.2	10.7
Femur Neck	6.5	15.2
Trochanter	1.4	8.9
AP Spine	1.4	14.1
Forearm	12.4	38.3
Any Site	13.3	41.3

Slemenda et al [6] showed that bone loss in older males correlated with declining estrogen levels more than testosterone, a surprising finding that since has been confirmed by others [7-11]; however, the correlations were only 0.1 to 0.3, indicating the bone loss was <u>not</u> closely associated with sex hormones. Estrogen use in transsexual males not only produced soft-tissue feminization, but increased BMD short-term [12]. However, BMD decreased to baseline levels after 2 to 5 years of estrogen use [13]. Endogenous androgen deficiency in adult males, however, does produce bone loss, as does androgen blockade [14]. Testosterone treatment corrects the bone deficits in hypogonadal men, but not in the older male with a subclinical deficit [15-25].

Men, unlike women, do not increase bone turnover as they age [11]. N-telopeptide levels are essentially constant from 30 to 90 years of age, and they are about 40% less than the levels seen in females [26,27]. **Even though turnover is low, antiresorptive therapy does increase BMD in older males [28]**. Osteoporosis in older men is often associated with secondary factors, such as alcoholism, corticosteroids, transplantation, and malabsorption [2,28]. The most common non-iatrogenic factor in males with fracture is a subclinical vitamin D deficiency that is associated with an elevated PTH and poor calcium absorption [29,30]. **Calcidiol is almost invariably under 20 ng/ml in male patients with fracture.**

The lifetime risks of hip fracture in men and women are close to the respective prevalence of femur neck BMD <-2.5 SD. Femur BMD in men is ~1 SD higher than in women which is commensurate with 2 to 3X lower risk. In females, the lifetime risk of clinical vertebral fracture is close to the 14% prevalence of spine BMD <-2.5 SD, but the prevalence for men is 10X lower. This accords with the clinical impression that vertebral fracture is rare in men. Surprisingly, mild morphometric deformation (-3 SD), and even one moderate deformation (-4 SD), is just as common in men as women. Apparently there is a different criterion for clinical deformity in men; men must have at least one -4.5 SD deformation, or two -4.0 deformations, before they can be classed as "fracture" cases. In addition, spine BMD may not be as good an indicator of fracture risk in men compared to women [5], because of sclerotic facets and osteophytes in men.

There are questions about the role of BMD, and of bone size, on fractures in males. **Since trabecular bone loss occurs at 1% annually in males as in females [4], the lower fracture rates observed in males seem to result from a combination of lesser loss of compact bone, and a greater bone size, than in females [31,32]**. Men with osteoporotic fracture have levels of BMD comparable to the low levels (spine BMD ~0.8 g/cm^2; femur neck BMD ~0.60 g/cm^2) of women who fracture [33,34]. The gradient of risk for fracture per unit axial BMD is similar in males and females, and because the BMD levels in young normal adult men and women are similar, the young normal reference values for women could be used with only modest error for men [5]. As is the case in women, men with fracture have 15% lower bone area and 30 to 40% lower BMC, i.e., men with small bones fracture [34]. **BMC is the most important factor in strength; BMD is needed to get a precise determination, and to partially compensate for body size. Most importantly, BMD does not obscure the important influence of size on risk, whereas a true volumetric density does.** For example, the volumetric density of vertebral bodies determined by computed tomography is higher in women than men at any given DEXA BMD [35]. Since the age-gradient of QCT density is identical in males and females, this implies that (a) there are sex-specific fracture thresholds using QCT that do not exist with DEXA, and that (b) bone size is responsible for much of the male-female difference in rates of true (clinical) vertebral fracture. **In fact, cross-sectional areas of the vertebral body are 25% larger in men than women [36], which undoubtedly protects men against fracture.**

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A Parable: Parameters or Variables?

Once there was a bone researcher who did not understand physical measurements too well. He knew that familiar characteristics such as age, body weight, and even bone density were called *variables*, but he didn't know what to call those attributes with which he was not familiar, so he used the term *parameters*. A *parameter* is actually a statistic (like the mean, SD or range) or a fundamental factor in a physical or mathematical model. When the researcher found out he was using a misnomer, he started using the term *variables*. A *parable* is a fictitious narrative illustrating a moral; it is not a concatenation of *parameter* and *variable*.

Secondary Hyperparathyroidism in Renal Disease

Adequate renal function is necessary for production of vitamin D, and when this is compromised, parathyroid hormone is elevated, particularly in the presence of elevated phosphorus [1] (see *LunarNews*, June 1998). The effect of hyperparathyroidism is often most evident in the compact bone [2,3]. **The focus on histomorphometry of trabecular bone has caused many to neglect the 10 to 20% decrease of axial BMD that is usual in dialysis patients, and the 3 to 4X increased rate of fracture.** Spine and femur BMD show annual decreases of 1 to 1.5% for each year on dialysis, and the changes are related to increases of alkaline phosphatase and PTH [4]. Ultrasonometry of the phalanges, tibia, and heel are all lower in dialysis patients [5].

The set point of parathyroid stimulation by serum calcium is normal in patients with renal failure [6]. Elevated serum phosphorous stimulates PTH secretion as much, or more, than low serum calcium [7]. One new approach to short-term (several hours) decrease of PTH is provision of calcium mimetics [8]. Treatment with active D-hormone provides longer-term (days) PTH suppression [8-10]. Patients with pre-dialysis disease and frank renal failure, and even transplant patients, require active D hormones. There has been some debate whether oral therapy is as effective as intravenous or intraperitoneal administration, but studies now show all three modes appear to be equally safe and effective [11]. **Treatment with D-hormone rapidly decreases PTH levels, and partially corrects the bone deficit.** Parathyroidectomy may be necessary in some patients if the glandular hyperplasia cannot be corrected, and the operation is usually associated with rapid increases of BMD [12].

Until recently, the treatment of patients with vitamin D hormone was compromised because of safety concerns. Calcitriol and 1α-D_3 resulted in frequent episodes of elevated calcium and phosphorous. This has been an acute problem in recent years because aluminum-based phosphate binders have been replaced by calcium binders which are less effective but avoid aluminum-induced bone disease. The above D-hormones in the presence of high calcium can cause hypercalciuria. New drugs, such as 1α-D_2, which will soon be available in the US and elsewhere, have at least a five-fold safety margin over calcitriol [13].

Renal transplantation can correct the skeletal problems associated with dialysis; bone mass increases and fracture rates decrease. However, bone gain may be minimal in some patients, and there may even be bone loss and increased rates of fracture due to use of corticosteroids and cyclosporine [14,15]. Treatment with antiresorptives to prevent post-transplantation bone loss is limited because they accentuate the secondary hyperparathyroidism already present [16]. Persistent elevation of PTH post-transplant reflects both pre-transplant hyperparathyroidism and vitamin D receptor polymorphism [17]. Dialysis patients who have PTH suppressed by D-hormone therapy pre-transplant have a better post-transplant prognosis. **D-hormone given post-transplant continues the PTH suppression, inhibits the bone loss due to immunosuppressants, and could prevent both graft rejection and infection [18].**

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Osteoporotic Fracture: BMD and Fracture History

The risk of fracture is influenced greatly by low bone mineral density (BMD) [1-4], and also by previous fracture [5-11]. **Even fracture in young adulthood doubles the risk of fracture later in life [6]. Patients with pre-existing fracture have several times the risk of subsequent fracture at any BMD.** It has been recognized for 20 years that hip fracture is associated with increased short-term morbidity and mortality, but it is now becoming clear that other fractures, and even low BMD, are associated with increased morbidity and mortality in the elderly [12-14].

Vertebral fractures, which typically occur in women after age 60, have been the traditional hallmark of osteoporosis; low spine BMD is the major risk factor. **Clinical vertebral deformation (i.e., requiring medical attention) increases short-term risk of fracture many times, particularly risk of vertebral and hip fracture [8]. Subclinical vertebral deformation is a less powerful but still significant predictor [9-11]**. It has been difficult to define vertebral fractures because the criteria are unclear, and because only about one-third of those defined morphometrically are of clinical significance. Only multiple, severe deformities have clear clinical correlates [11,15]. Melton et al [16] found that the conventional morphometric definition using -3 SD deformation did not produce an increased risk with age. **However, "severe" fracture (one -4 SD, or two -3 SD deformations) was associated with a pronounced aging increase of risk (Figure 1)**. MXA can be used to identify these significant (-4 SD) deformations with a precision comparable to radiographic morphometry, yet with much greater ease and much lower radiation dose [17,18].

Fractures of the proximal femur have become the predominant index of osteoporosis in the past 10 years, with the realization of their morbidity and high cost ($30,000 to $40,000). These fractures typically occur after age 75 years in both men and women. The lifetime risk of a hip fracture is about 5% and 15% in men and women, respectively. Low femur BMD is the major risk factor in subjects

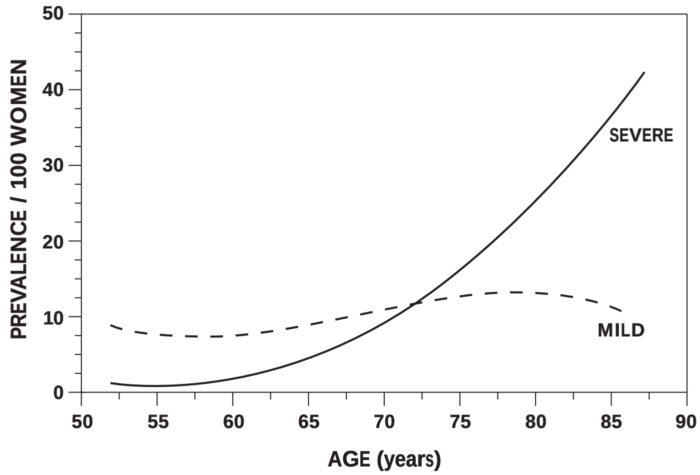

Figure 1. There is an increase of moderate vertebral deformation with age in women, but not of mild (one -3 SD) deformation; adapted from Melton et al [16]

under age 80, and the gradient of risk (3X per 1 SD change of BMD) is the same in men and women [3,4]. BMD remains important after age 80 (Figure 2), but frequency of falling is just as important [1,2].

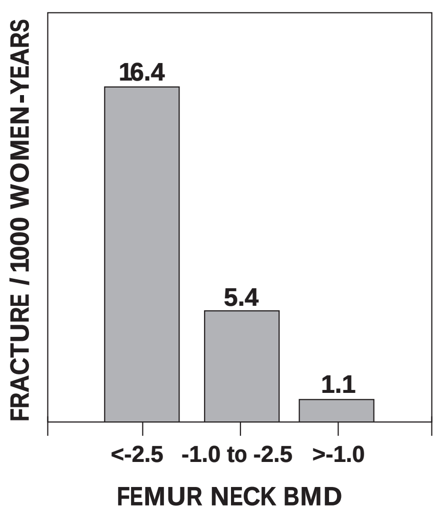

Figure 2. Incidence of hip fracture at different levels of femur neck BMD in EPIDOS [1].

Various assessments of factors affecting the risk of hip fracture have appeared recently. **Use of tranquilizers, antiepileptic drugs, and antidepressants greatly increases the risk of falling and of hip fracture [19-23].** Lesser use of such medications, higher levels of physical activity, and better neuromuscular control, may contribute to lower rates of hip fracture in some populations, such as Hispanics [24]. Asians who have lower BMD values than whites have lower hip fracture rates, apparently because they fall only half as often as elderly whites [25]. Falls, and particularly falls to the side, may be associated with muscle weakness, inactivity, and poor neuromuscular control, as well as with medications [23,26,27]. Previous fractures of the lower limb, and in fact any lower limb injury, greatly increase the risk of a subsequent hip fracture [5,26]. Moreover, bone loss occurs in the proximal femur of the affected limb, reaching 5 to 10% after one year [28]. **The presence of any lower limb dysfunction or fracture in the patient's history is justification for measuring the affected femur, or possibly both femora**. Anisomelia in os calcis BMD, or more importantly Stiffness, is one of the better indicators of a potential increased risk.

Loss of body weight in the elderly, a common phenomenon in western societies, is associated with increased risk of fracture [29-32]. Such weight loss is often a sign of disability, and may be associated with an increased propensity to fall, but there is also a direct association of low weight with low femur BMD [32].

About half of the fractures occur in the institutionalized elderly, and are associated with vitamin D deficiency. These are readily correctable in many cases with vitamin D supplements or active vitamin D. The other half occur in the elderly and can be prevented cost-effectively by targeting

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Osteoporotic Fracture *from page 9*

the population at high risk. **Targeting of therapy to those at the highest risk reduces the effective cost of treatment per fracture prevented [33,34].** Use of age and body weight as predictors of risk is just as effective as more complex clinical schemes [35].

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Osteopenia with Anorexia/Bulimia

Bone loss and fractures are associated with anorexia. Loss of body weight (usually 10 to 15 kg of fat) in obese patients is normally associated with only a 1% loss of total skeletal mass (see *LunarNews*, August 1997). **Even normal-weight individuals who lose up to 10 kg do not show bone loss**; this has been observed during extreme training of special forces recruits in the armed services. However, "normal" women who lose most of their fat, and even some of their lean soft tissue, as a consequence of anorexia, show much greater bone loss [1-15]. **Anorexia produces a 50 to 80% reduction from normal fat mass, and up to a 10% reduction in lean tissue. This fat loss is associated with a 15% reduction in regional BMD and a 30% reduction in total body bone mass**. Anorectic young women have T-scores of an older osteoporotic. Bone resorption is greatly elevated, and formation is depressed, due in part to a compromised pituitary axis, and decreased estrogen; **most anorectics are amenorrheic**. In addition, the "starvation" diet of anorectic women often produces excess acid which could contribute to bone loss. The loss is greater than in other groups of amenorrheic women, for example excessive exercisers who have hypothalamic amenorrhea. Correction of the dietary component and treatment with estrogens both can help correct the BMD deficit, but full normalization is rarely achieved, perhaps because bone formation is not increased. In contrast to anorexia, **bulimia tends to produce only a 10% reduction in fat mass, and is associated with only a 5% reduction of BMD [16,17].**

A recent report by Gordon et al [16] showed that treatment of anorexia with moderate doses **(50 mg/day) of dehydroepiandrosterone (DHEA) both decreased bone resorption markers and increased bone formation**. Menstruation resumed in over half of the subjects. DHEA appeared to be safe and well-tolerated, but did not by itself increase BMD.

Table 1. Comparison of BMD decreases in anorexia and bulimia in young women (age 18 to 29 years); adapted from Sundgot-Borgen et al [15].

	ANOREXIA (n=13)	BULIMIA (n=43)	CONTROL (n=17)
Weight (kg)	44.8	58.5	62.6
Fat %	13.5	22.9	25.9
BMD (g/cm^2)			
Total Body	0.93	1.14	1.21
Lumbar Spine	0.78	1.15	1.21
Femur Neck	0.72	1.05	1.08

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Body Composition by DEXA: Ready for "Prime-Time"

A recent editorial by Marta van Loan [1] concluded that DEXA "is ready for prime time when it comes to overall clinical evaluation of body composition." This is because DEXA provides a direct indication of bone, fat, and lean tissue. **DEXA, unlike dilutional methods, underwater weighing, and neutron activation analysis, does not depend critically on now disproven assumptions about (a) the constancy of elemental composition, (b) the invariance of water in lean tissue, or (c) the invariance of bone in fat-free mass [2]**. Moreover DEXA, unlike all other methods, provides regional information that is critical for many clinical and sports medicine applications. DEXA results provided by the DPX densitometer have been validated by direct carcass analysis in several studies (usually on pigs). **A recent study by Elowsson et al [3] showed the DPX accurately measured composition in piglets weighing between 14 and 22 kg despite variable water-content of lean tissue**. The correlation between chemically determined mass and DEXA values was >0.99 for lean tissue mass and bone mass, and 0.95 for fat mass. Even small changes of fluid content can be accurately measured by DEXA. This high accuracy has allowed DEXA to be used as a reference method against which other non-invasive methods are evaluated [4-9].

The DPX has been validated not only in humans, but in smaller animals, such as piglets (approximating newborn infants) and rats weighing from 200 to 700 g. There have been uncertainties whether the QDR instruments can be used for these smaller animals; in rats the QDR systematically overestimates the fat content by 30 to 40% and underestimates both chemically-determined lean tissue and ash content [10,11]. The QDR also was highly inaccurate for both bone and body composition in piglets [12].

The initial composition applications of DEXA were for monitoring compositional alterations in obese subjects during dieting [13-16], but increasingly there are applications in sports medicine. The ability of DEXA to provide regional values is particularly important in relation to exercise studies. For example, athletes have been shown to hypertrophy both muscle and bone in the exercised area (typically the legs). Women who exercise tend to avoid the usual aging increase in body fat, and, in particular, they do not significantly elevate central adiposity [17]. Older men and women with high fat content have threefold more disabilities [18]. Lean tissue mass is relatively constant with aging in both retrospective [19-21] and longitudinal [22] studies. The apparent decrease of ~500 g between young and elderly women in lean tissue may be a cohort effect, and simply reflect the smaller body size of the latter group. There are conditions in which lean tissue is lost, for example with growth hormone (GH) deficiency, corticosteroid excess, or immobilization. Bedrest for 6 weeks causes loss of lean tissue from the legs, but not the arms [23].

There are "clinically" relevant applications of body composition, particularly in relation to GH deficiency [24-27]; treatment with GH increases lean tissue and decreases fat mass, particularly abdominal concentrations. One possible application of GH therapy could be in patients who are cachexic, or who are protein depleted [28,29]. Jensen et al [30] studied GH treatment of colitis patients who had received an ileostomy. A short-course (1 week) of GH helped prevent loss of lean tissue. Patients with chronic obstructive pulmonary disease often are cachexic. Engelen et al [31] showed such patients had 8% lower lean tissue mass than controls, but higher fat content, and a 10% BMD deficit. These alterations are consistent with both corticosteroid treatment and restricted physical activity. Hyperthyroid patients also may have reduced lean tissue mass, and compromised bone. Treatment of hyperthyroidism not only increased total body BMC and BMD by 5% over 12 months, but significantly increased lean tissue mass [32].

There have been technical limitations in using DEXA for body composition. Wide-angle fan-beams cause distortions at the edge of the field as well as magnifying the tissue closer to the source more than that closer to the detector. The QDR fan-beam densitometer has a major magnification error. There were significant differences of fat mass, lean tissue mass, and bone mass between supine and prone positions [33]. The differences would be even more dramatic in heavy subjects. As a consequence of these problems, **over 90% of composition researchers use pencil-beam densitometry**. Ellis et al [34] compared the QDR pencil-beam and fan-beam densitometers and found significant differences for soft-tissue composition, but not for bone. **The new LUNAR PRODIGY densitometer avoids the distortions of a wide fan-beam through use of a narrow fan-angle**. There are no differences between pencil-beam DPX and fan-beam PRODIGY results for either bone or soft-tissue composition.

One major new development has been a phantom for body composition studies [35]. This has been shown to be useful in cross-calibrating different instruments, and for quality assurance in longitudinal studies [35,36].

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Corticosteroids and Bone

Use of high-dose oral corticosteroids is associated with profound bone loss [1-7]. The skeletal effect is mediated by osteoblast differentiation, and accelerated apoptosis of osteoblasts [8,9], but there is little evidence of increased bone resorption. In contrast, methotrexate appears to decrease resorption and increase bone formation [10]. The adverse corticosteroid effect on formation probably explains why skeletal growth is inhibited in children. Interestingly there is little or no skeletal effect of inhaled steroids in adults [11], and even little effect in children at low doses [12], but there may be effects on skeletal growth at higher doses [11,13,14].

There is substantial disagreement about whether bone quality is compromised by corticosteroids, and if so, in what way. A prominent study by Peel et al [15] showed that the fracture rate for patients on oral corticosteroids was twice that expected at any given BMD level. Several studies presented at the ASBMR/IBMS meeting suggested that women taking corticosteroids have an elevated fracture risk even after adjustment for BMD [16-19], but one study [20] found that this was not the case. More detailed, large-scale studies need to be done to show a fracture effect independent of BMD.

There is a surprising amount of variation in physician concern and action about corticosteroid-induced osteoporosis. Buckley et al [21] recently surveyed about 200 physicians. The specialties (gastroenterology, nephrology, rheumatology, pulmonology) that use steroids have varied opinions about the importance of osteoporosis and its prevention. Clinicians are learning to control steroid dosage and to use alternatives such as deflazacort that produce less bone loss, as well as less increase in body fat and lipids [22].

There is growing consensus that bisphosphonates are effective in preventing corticosteroid-induced bone loss [2]. Alendronate seems to be most favored today, but etidronate has also been widely used. Recent studies have shown that risedronate and other bisphosphonates not only increased axial BMD, but prevented fractures. **Consequently, all bisphosphonates today seem to be acceptable as a therapy in corticosteroid-treated patients.**

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Physical Activity: Greater Effects on Muscle Than Bone

Physical activity clearly has a positive effect on both muscular and skeletal growth [1]. Growing athletes show hypertrophy in both muscle and bone that persists into adult life and perhaps into old age provided the exercise is weight-bearing. Exercise that is not weight-bearing (horseback riding, swimming) increases muscle size and strength [2,3] but has no effect on bone [4]. This hypertrophic response to exercise still exists in young adults, but it is greatly attenuated [5,6]. **Older adults show even less of an adaptive response, and several studies have concluded that postmenopausal women show no positive skeletal response to exercise [7].** A recent study by Bassey et al [8] demonstrated that exercise which produced a positive musculoskeletal effect in premenopausal women had no effect in postmenopausal women. Older men and women who are athletic [9,10] lose bone at the same rate as nonathletes, suggesting that sustained exercise has little preventive effect on most bones. Physical activity does, however, have an effect on the os calcis. **BMD and ultrasound measurements of the os calcis are invariably higher in active versus inactive persons and are particularly elevated in athletes [11-13] (see Table 1)**.

The influence of activity on heel Stiffness may be one reason why it indicates risk of fracture independently of BMD. **Older subjects who are inactive have a greater (30 to 40%) risk of hip fracture than their active peers [14-17], but there is no advantage of more than moderate activity [16]**.

The mechanism by which activity prevents fracture may be through muscular size, strength, and coordination rather than through bone itself. If this is the case, then os calcis Stiffness would be a marker for the latter factors rather than increased axial BMD. **Exercise and physical activity can maintain neuromuscular coordination, limit body sway, and potentially prevent falls [18]. Physical activity in the elderly may be far more positive for these latter factors than for the skeletal component itself.**

Table 1. Stiffness of the os calcis was greatly increased in female runners versus controls in two independent studies; the spine was not increased significantly, total body BMD was 3 to 4% higher, femur neck BMD was 10% higher, and Stiffness was 22 to 26% higher.

	Gomez A. et al [12]			Brahm et al [13]		
	Runners	Controls	Runners/ Controls	Runners	Controls	Runners/ Controls
Spine BMD	1.25	1.23	1.02	1.23	1.23	1.00
Total Body BMD	1.20	1.15	1.04	1.26	1.22	1.03
Femur Neck BMD	1.08	0.98	1.10	1.16	1.05	1.10
STIFFNESS-Os Calcis	117	93	1.26	118	97	1.22

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Ultrasonometry: Only Achilles Provides Valid WHO T-Scores

Ultrasonometry has now come of age [1]. There are over 5000 ultrasonometers in the world of which 4000 (80%) are used for measurement of trabecular bone of the os calcis. The remaining 1000 units are used to measure speed of sound (SOS) at the surface of compact bone in the tibia, finger, and forearm. The diagnostic sensitivity of those latter devices is extremely poor [2,3], a deficiency which is due only in part to their poor precision. Rather, SOS measurements on compact bone show the same poor diagnostic sensitivity associated with tibia, finger, and forearm BMD. SOS on the latter sites correlates very poorly (r~0.2) with failure loads of axial bone. Blanckaert et al [3] recently reported a detailed comparison of phalangeal SOS, axial BMD, and Stiffness on the heel. The latter two measurements were twice as sensitive as phalangeal SOS (Table 1). Mallmin et al [2] found a similar lack of sensitivity for phalangeal SOS in relation to hip fracture. **The Z-score for finger SOS is usually normal in fracture patients, averaging 0.7 to 1.0 SD higher than that for axial BMD or Stiffness.**

Table 1. Z-scores comparing osteoporotic patients, or corticosteroid-treated patients, and age-matched controls; from Blanckaert et al [3,13].

	Osteoporotic	Steroid
Phalangeal SOS	-0.4	—
Spine BMD	-0.9	-0.6
Femur BMD	-1.1	-0.6
Os Calcis BUA	-1.0	-0.7
Os Calcis SOS	-0.9	-0.8
Os Calcis STIFFNESS	**-1.1**	**-0.8**

New studies are showing that ultrasound measurements on the heel predict failure loads of both the proximal femur and vertebra as well as DEXA measurement of axial sites [4,5] (Table 2). The correlations are better for femoral neck fractures than spine fractures, but the diagnostic sensitivity of ultrasonometry *in vivo* is high for both types of fracture. Of course, the BMD and BMC measured directly on the excised spine or femur correlates far more highly with its strength (r~0.9), but the presence of soft-tissue decreases the accuracy of DEXA and compromises the correlation. Ultrasonometry measures trabecular bone of the os calcis directly, with little interference from overlying soft-tissue; this may be one reason for the better diagnostic sensitivity of heel ultrasonometry. BUA, SOS, and Stiffness of the os calcis correlate highly (~0.85) with BMD of the purely trabecular bone [6,7]. **BUA largely reflects BMD rather than structure [8,9]. Wu et al [8] showed, through progressive demineralization of trabecular cubes, that BMD and BUA decreased concomitantly and proportionally to the amount of mineral present. In contrast, SOS reflects trabecular connectivity [10]**. This may be one reason that Stiffness, which includes a contribution from SOS, gives better sensitivity than BUA.

*Table 2. Correlation of failure load of the femur [4] and spine [5] with BMD and ultrasonometry on 58 cadavers (*p<0.01; **p<0.001).*

SITE	Variable	NECK FX	SPINE FX
Spine	BMD	0.46*	0.53**
	BMC	0.65**	0.62**
Neck	BMD	0.68**	0.41*
	BMC	0.71**	0.46*
Os Calcis	SOS	0.65**	0.48**
	BUA	0.71**	0.27^{LS}
	STIFFNESS	**0.75****	**0.40***

All ultrasonometers that measure the heel have good diagnostic sensitivity, although only a few comparisons have been done [10-14]. The Z-score comparing osteoporotics to age-matched controls is about -1 using Stiffness with Achilles. Other ultrasonometers produce Z-scores from -0.5 to -0.8. In part, the better sensitivity of the Achilles is due to slightly better diagnostic sensitivity achieved by Stiffness than BUA or SOS alone [11-17]. **The combination of BUA and SOS provides a better indication of bone strength *in vitro* than either variable alone [18,19].** Until recently the better sensitivity of Stiffness had not been demonstrated conclusively *in vivo*, although several studies had suggested higher Z-scores for Stiffness than BUA or SOS. In the study by Cepollaro et al [17], the gradient of risk for vertebral fracture using Stiffness was significantly greater than that for BUA or SOS alone. **A study by Hadji et al [20] presented at the ASBMR showed that the area under the ROC curve was significantly greater for Stiffness than for BUA or SOS.**

Prospective studies have demonstrated an excellent gradient of fracture risk for heel ultrasonometry in older women, but there have been few studies done in patients <65 years of age. Some uninformed critics have even suggested that ultrasonometry might not prove diagnostic in younger patients. Thompson et al [21] presented a retrospective study showing that Stiffness provided a good Z-score (-0.8) in that immediate post-menopausal population. **A prospective study by the same group now indicates that Stiffness predicts incident fracture in that age period [22]. The Achilles is the only ultrasonometer documented to predict fracture in the first postmenopausal decade.**

There also are an increasing number of studies on younger patients with corticosteroid osteoporosis [13,23,24]. Corticosteroids cause loss of bone, but also increase the risk of fracture at any given BMD level, so fractures typically occur at age 60, rather than after age 70 as is the case in postmenopausal osteoporosis. Blanckaert et al [13] showed that the Z-score for Stiffness was -0.8 in patients compared to matched controls; this was more diagnostic than spine or femur BMD which had a Z-score of -0.6. Similarly, Oliveri et al [23] showed a Z-score of -1.3 for Stiffness compared to about -0.9 for axial BMD. **The Achilles is the only ultrasonometer with documented sensitivity in corticosteroid osteoporosis.**

Ultrasonometry of the os calcis provides some independent information on risk of fracture beyond that afforded by BMD itself. Yeap et al [16] stratified postmenopausal women with and without fractures by BMD level and found that Stiffness was

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Table 3. Comparison of Stiffness in osteoporotic women with fractures to unfractured controls matched for femur neck BMD. The results are given for the controls within 3 years since menopause (YSM) and more than 10 years since menopause. The osteoporotic women were almost 1 SD lower in Stiffness even after BMD matching. Adapted from Yeap et al [16].

Neck BMD	YSM<3	YSM>10	Osteoporotic
<0.6 g/cm^2	73.5	72.3	60.8
0.6 to 0.7 g/cm^2	83.1	81.5	71.5

Table 4. Prevalence (%) of cases with T-score below -2.5 SD with different measurements.

	Age (Years)		
	50-59	60-69	70-79
Axial BMD	5	18	33
STIFFNESS	4	17	32
Forearm BMD	2	15	52
BUA	2	4	15
QUI/eBMD	2	5	14
Finger BMD	1	2	10

about 1 SD lower in the fracture patients even after "BMD-matching" (Table 3). As yet, this advantage has not been translated into a lower composite Z-score. It does mean, however, that the number of abnormal cases (below -2.5 SD) is increased greatly (from ~20% to 30% of postmenopausal women) when both Stiffness and axial BMD are used as diagnostic criteria. It is unlikely that the independent information on fracture risk derives from any relation to bone structure. Rather it may reflect the fact that ultrasonometry of the heel is an excellent indicator of integrated physical activity (see Physical Activity, this issue), which in turn halves the risk of fracture.

A key factor in all densitometry, including ultrasonometry, is the ability to use the WHO T-scores in assessing women at risk. Most heel ultrasonometers utilize BUA as their output variable, or produce indices such as QUI which depend almost wholly on BUA. However, BUA and QUI declines by only 1 SD (about 15%) with age (Figure 1), so that the T-score for BUA with all heel ultrasonometers, including the Achilles, is only -1 at age 65. As a consequence, the WHO criterion for osteopenia is not achieved until that age, and the WHO criterion for osteoporosis (-2.5 SD) is almost never achieved. **The Sahara, DTU-One, UBIS, and other similar devices show an average T-score of -1 in the elderly, and the prevalence of osteoporosis is only about 5% in postmenopausal women (Table 4)**. This compares poorly to the T-score of -1.6 using femur BMD or Stiffness (Achilles) and a 15 to 20% prevalence of osteoporosis [15,25]. Stiffness gives the same prevalence of abnormal cases as axial BMD in older women as well [25]. **Of all heel ultrasonometers, only the Achilles provides T-scores concordant with the WHO criterion of osteoporosis.**

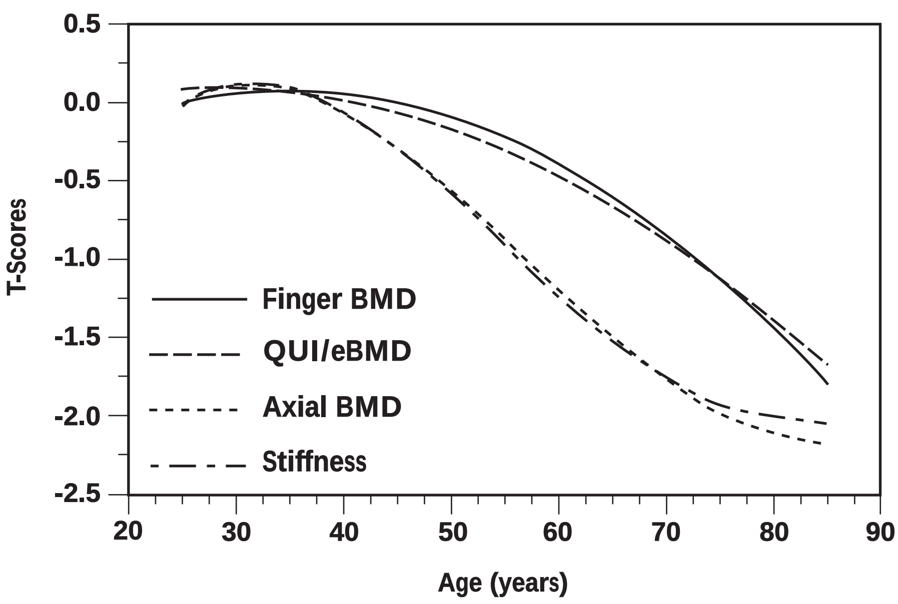

Figure 1. The decrease of os calcis Stiffness (Achilles) with age in normal postmenopausal women closely approximates axial BMD by DEXA. The QUI/eBMD (Sahara®) approximates finger BMD (accuDEXA®) and gives T-scores that are at least 0.5 SD higher between age 50 and 70 years.

Ultrasonometry of the os calcis has been shown to give a response to therapy similar to spine and total femur BMD. **The precision error of ultrasonometers that use fixed transducers, with a waterbath or a bladder, is about half that of contact ultrasonometers with moving transducers (2% versus 5% in elderly subjects) [26-30]. The "better" precision of imaging ultrasonometers (~2%) is more a function of their using fixed transducers with good coupling rather than better location of the ROI [31]**. Contact ultrasonometers cannot accurately measure SOS because they must measure heel width accurately to get a result. **The error in heel width measurement is 1 to 2 mm out of 40 mm, so there is an inherent uncertainty of 2 to 5% in SOS measured with contact ultrasonometers**. This error is compounded by the large effect of edema on results (5 to 15%) [32]. Even post-exercise edema in the heel adversely compromises both BUA and SOS [33,34]. These systematic errors, as well as the high precision error (4 to 8%), prevent contact ultrasonometers from being used to monitor bone loss or the response to therapy in the individual patient. In contrast, the Achilles can be used to monitor even short-term changes [28].

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Biochemical Markers: Research Tool Fails in Clinical Practice

There have been many published studies on the research use of biochemical markers of bone over the past 5 years, largely stimulated by a cabal of scientists with secret commercial interests. Bone turnover and biochemical markers of turnover are increased during growth and after the menopause; turnover increases in response to stimulatory agents and decreases with antiresorptive therapy [1-16]. Despite the obvious trends, several major problems inhibit the clinical use of biochemical bone markers: (a) geographic and ethnic differences, (b) circadian rhythms, (c) assay variation, and most importantly, (d) a large biological variability [17-29]. **Reports from the ASBMR/IBMS meeting in San Francisco may sound a death knell for the marker industry and its marketing campaign. Several reports demonstrated that the intra-individual variation of urinary markers is very high (15% for pyridinoline and deoxypyridinoline; 20 to 50% for telopeptides), thereby preventing their use to indicate either bone loss in untreated patients or the response to therapy in treated patients.**

Many groups have now examined the long-term variability of markers. Investigators from the University of Sheffield (UK) [19,20] found that the precision for urinary telopeptides was 24 to 48% over 1 to 5 years, while that of deoxypyridinoline was 15%. They concluded that *"a single measurement of a marker of bone turnover in individual postmenopausal women cannot be used to predict her bone turnover in subsequent years"* [20]. **The authors opined that markers could have a role in monitoring response during the first 6 months of antiresorptive treatment, but concluded that the large intra-individual variability over 2 to 5 years precluded use of markers to monitor therapeutic responses**. Beck Jensen et al [24] followed 21 women over 30 months; the precision of deoxypyridinoline was about 20%, but the precision for telopeptide determinations was over twice as large (49%). Smaller errors (10 to 15% for deoxypyrodinoline and 20 to 35% for telopeptide) have been reported, provided samples are stored and assayed at the same time from the same kit [25-28], a practice that is not possible in clinical practice. **Reports show that there are large differences among assay kits (6 to 13%) that preclude long-term precision even on the same sample [24,25,28]**.

Table 1. The coefficient of variation (%) for bone markers shows high intra-individual (day-to-day) variability over time.

SERUM	24 MONTHS Hannon et al [19]	30 MONTHS Beck Jensen et al [24]
Osteocalcin	7.2	16.4
Alk phosphatase	9.0	7.7
TRAP	5.4	--
URINE*		
Calcium	32.6	44.1
Hydroxyproline	27.2	46.7
Pyridinoline	10.9	19.6
Deoxypyridinoline	15.4	18.4
N-telopeptide	24.3	48.9
C-telopeptide	47.7	–

*relative to creatinine

Previous reports on markers in the *LunarNews* have summarized studies showing the variability in urinary markers of resorption is several times greater than that for serum markers of formation. Assays for resorption markers in blood have been awaited for several years. The first studies have shown a reduced variability, but also a reduced response to therapy, so the signal-noise ratio may not be better than that for urinary markers [30,31]. Again, differences among assay lots over time may exacerbate the large day-to-day variability and further compromise clinical use.

Can markers predict bone loss in untreated patients? Many experts now point out that the low correlation between markers and BMD indicates a high prediction error for individual cases. A few researchers who have not differentiated the group response in turnover from the individual response have made speculations with regard to the predictability of response [27,32]. The correlation between marker levels and bone loss is poor in untreated women (r=0.3), and long-term bone loss cannot be predicted. **Typically markers explain less than 10% of postmenopausal bone loss [33-38]. Body weight correlates better with BMD, and with postmenopausal loss of BMD, than do biochemical markers [39].**

Can markers predict bone increase in treated patients? The correlation between marker change and BMD increase is low and prediction error is high. Greenspan et al [32] recently reported that the decrease in urinary markers of resorption at 6 months in women treated with alendronate "predicted" long-term changes of BMD; however, the correlations in this case averaged only about -0.3. Only 10% of the variation in BMD response was therefore predicted by the marker change. Both osteocalcin and telopeptide were better markers than deoxypyridinoline and bone alkaline phosphatase in this study, but in other studies, exactly the opposite has been observed. Typically patients treated with antiresorptives show a decrease in telopeptides that is double that of deoxypyridinoline, but since the precision error of the former is twice that of the latter, the telopeptides offer no advantage. The confidence interval in predicting BMD change typically is identical to the confidence interval of the change in the treated group. **In essence, the changes observed in biochemical markers simply confirm that the patients took the drug and do not indicate differences in responsiveness that could be construed as "predictive accuracy" of BMD response.** If these decreases of urinary resorption markers in response to antiresorptives were in fact predictive, one would expect them to be equally predictive with resorptive agents other than alendronate. Greenspan et al [32] indicate that a 30% decrease of telopeptide at 6 months predicts a 3 to 4% increase in femur BMD, and a 6% increase in spine BMD over 2.5 years. However, calcium supplementation at 1000 to 1500 mg/day produces a 15% decrease in urinary deoxypyrodinoline and a 30% decrease in telopeptide levels [40,41]; these decreases are not associated with increases of femur or

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spine BMD. Another problem is that of "time course"; **resorption markers reach their nadir at 6 months, but axial BMD may increase over 3 to 4 years thereby complicating any simplistic interpretation.**

Ott et al [42] examined changes of urinary markers and 4-year changes of BMD in a large group of women treated with alendronate or calcium. **Baseline levels of markers did not correlate with response. Moreover, changes occurring in the untreated group did not predict long-term BMD outcomes, nor did the decreases in marker levels associated with alendronate treatment correlate well (r=0.2 to 0.3) with BMD changes.** Ott et al [42] concluded that the ability of baseline markers to predict subsequent changes of BMD "*is very limited and not clinically useful. These markers cannot be used to select patients who are more likely to respond to alendronate. The markers decrease dramatically with alendronate therapy, but the relationship between the one-year change in the markers and the four-year change in bone density is so modest that it is not clinically helpful in the management of an individual patient.*" A recent review concluded that *"the variation seen in results obtained is so wide that reliability and a willingness to trust the test results is difficult"* [43].

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PIXI: Fast, Precise Measurements

The PIXI densitometer was introduced over a year ago and now is recognized as the standard for DEXA of the peripheral skeleton. The unique cone-beam geometry coupled with a CCD area detector provides an image of the os calcis or distal forearm in **only 5 seconds**. The PIXI has won acclaim not only in clinical management, but in population studies where large numbers of individuals need to be measured. In such “screening” situations, **the typical load in a standard work day is 200 to 300 cases**. At the ASBMR meeting, researchers from Helen Hayes Hospital [1] reported excellent precision on phantoms (0.5%), as well as reasonable precision *in vivo* (1.7%). German researchers found similar precision *in vitro* and slightly better (1.3%) precision *in vivo* [2]. The T-score on the os calcis correlated highly with that on the femur neck (r=0.77). Interestingly, the kappa coefficient, showing concordance between T-scores below -2.5 on the heel and on the femur neck, was 0.49 [1]. This is even higher than the kappa of -0.4 between spine and femur. Obviously, the heel is not completely concordant; however, other measurements on the femur, such as the trochanteric BMD, are even less concordant (kappa 0.3) with the femur neck.

There are now indications that measurements on the os calcis provide independent information on risk of fracture, probably because they reflect the integrated effect of recent physical activity. Patients with a high level of physical activity tend to maintain os calcis BMD (and bone ultrasonometry values). Thus os calcis BMD can be used not only for screening purposes, but to provide incremental information on risk of fracture in patients. In the screening situation [3], a relatively normal BMD (T-score -1.2) is used to define the lowest half of the postmenopausal population. This allows concentration of axial densitometry on those most at risk.

A special model, the PIXI$_{\mathrm{MUS}}$™, is available with lower-energy and smaller pixel size (0.18 x 0.18 mm) to better image the small, low-density bone of mice. Total body bone mineral and body composition can be determined reliably (<2% precision) in under 5 minutes. Femur BMD also was measured with 2% precision *in vivo*. Rectilinear DEXA scanners for measuring mice take about 30 minutes, have poor spatial resolution and unacceptable (>5%) precision [4].

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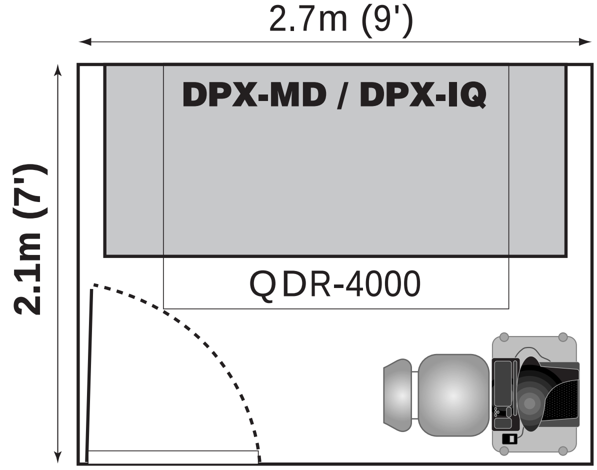
LUNAR: The Total Solution is Space Efficient

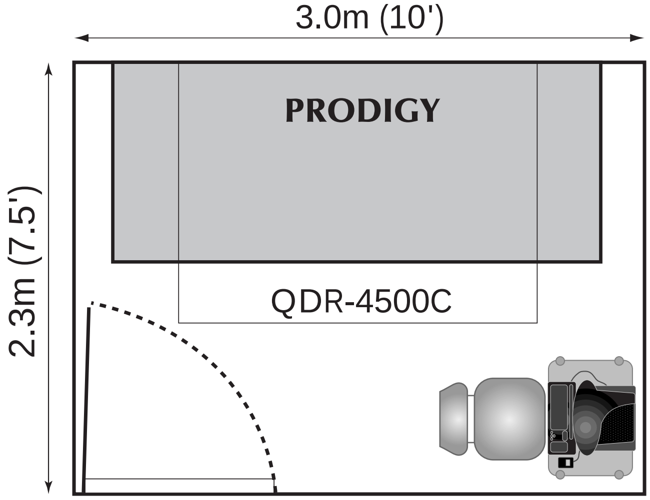
All DPX and PRODIGY densitometers come standard with the capability for total body measurement. Total body BMD and soft-tissue composition are the fastest growing segments of densitometry practice. The DPX-MD and DPX-IQ pencil-beam densitometers actually require the same space as partial-body devices (QDR-1000/QDR-4000). The full-featured PRODIGY fan-beam densitometer requires the same space as the QDR-4500C, and much less (40%) space than the total-body QDR-4500W (2.8 versus 4.5 m²).

	FOOTPRINT		AREA		ROOM-SIZE	
	Metric (*cm²*)	English (*inch*)	Metric (*m²*)	English (*ft²*)	Metric (*meter*)	English (*feet*)
DPX-Compact	183 x 97	72 x 38	1.8	20	2.1 x 2.1	7 x 7
DPX-Full	242 x 101	95 x 40	2.5	26	2.1 x 2.7	7 x 9
QDR-4000	183 x 132	72 x 52	2.4	26	2.4 x 2.4	8 x 8
PRODIGY	263 x 111	113 x 44	2.9	31.2	2.3 x 3.0	8 x 10
QDR-4500C	202 x 140	80 x 55	2.8	30.5	2.4 x 2.4	8 x 8
QDR-4500W	302 x 150	119 x 59	4.5	48.8	2.7 x 3.6	9 x 12

Pencil-Beam Densitometers



Fan-Beam Densitometers



President's Letter

Dear Colleagues,

The past year has been a momentous one for bone densitometry and for LUNAR. Dual-energy x-ray absorptiometry (DEXA) of the axial skeleton is recognized as the gold standard of diagnosis. At the same time, ultrasonometry of the os calcis has been further validated to provide an independent indicator of fracture risk. **Ultrasonometry can be used not only as a low-cost surrogate for axial BMD, but to provide incremental information to better target therapy**. Finally, the Achilles has now been shown to have precision comparable to axial BMD for monitoring therapy. The world-leading Achilles+ ultrasonometer was approved for sale in the US in June 1998, and reimbursement for the ultrasonometry test (CPT 76977) has been set at $41.

A new concept in DEXA was introduced by LUNAR in December 1998 with the PRODIGY. This state-of-the-art densitometer provides fast (30-second), low-dose measurements. It is the first and only densitometer providing total automated densitometry of the spine and femur including DualFemur™. PRODIGY eliminates the difficulties of both set-up and analysis of older instruments. PRODIGY provides total body bone density and body composition in under 5 minutes. **Total body scanning is the fastest growing modality for DEXA**. Over 90% of clinical trials in osteoporosis require total body scans as a safety endpoint, and extensive research is being done in other areas (growth hormone, corticosteroids, sports medicine) that demand body composition. Clinical use of total body BMD is needed for pediatric studies, renal disease, hyperparathyroidism, and gastroenterology. LUNAR has met this fundamental need by providing total body capability in our four densitometer models (DPX-MD, DPX-IQ, PRODIGY, EXPERT-XL) at no extra cost. If you are currently considering a compact (spine/femur) densitometer, contact your local LUNAR sales representative or distributor to get a full-size model at no extra charge. **Don't get "caught short" in the next millennium with only spine/femur scans.**

Richard B. Mazess, Ph.D.

Forearm BMD: Insensitive Before Age 65

Forearm densitometry does have some value for diagnosis of bone disease, although it cannot be used for monitoring treatment [1]. **Over the past 20 years, numerous studies have shown that forearm BMD has only half the sensitivity of spine/femur BMD in identifying patients with osteoporotic fracture (vertebral, proximal femur) prior to age 70 years [2-4].** The study by Mautalen et al [4] showed that patients with vertebral fracture had low spine BMD regardless of age (~0.8 g/cm^2 giving an average T-score of -3.2). Women 50 to 59 showed twice as much spine loss, in terms of both percentage and Z-score, as radius diminution (Table 1). After age 70, however, radius loss caught up to the spine loss in the osteoporotic women.

Proponents of the forearm have obscured this deficiency by including less serious fractures (ankle, forearm) and older patients in their analyses. In patients over age 70, the forearm, and other peripheral sites, are as sensitive as spine BMD for fracture in general [5]. However, hip fracture is critical in older patients; femur BMD is far more sensitive for this. The os calcis is the most sensitive peripheral site for risk of both femur and vertebral fracture; forearm BMD is particularly useful in relation to forearm fractures [6,7]. Forearm BMD predicts hip fracture in the elderly, only because it is a marker for femoral bone loss. Researchers at UCSF recently confirmed that forearm BMD (and also trabecular density by pQCT) was much less predictive of hip fracture than femur density [8]. Tibial ultrasonometry also was not predictive of hip fracture.

Table 1. BMD as a percent of controls (%) and Z-score (Z) in fracture cases compared to matched controls. From Mautalen et al [4].

	RADIUS		SPINE	
AGE	%	Z	%	Z
50-59	-9.5	-1.2	-25.0	-2.5
60-69	-16.2	-2.0	-19.3	-2.2
70-79	-21.3	-2.5	-19.8	-1.8

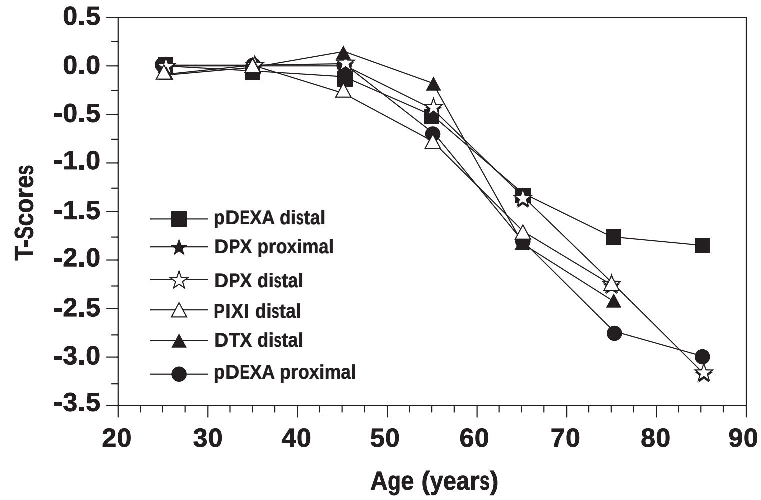


Figure 1. Different forearm densitometers produce a relatively similar decrease of T-score with age in normal females [13,14].

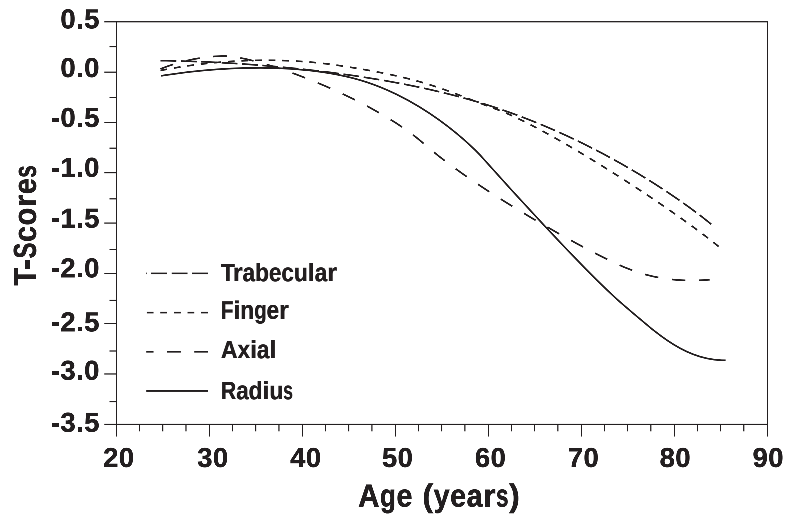


Figure 2. The changes of T-score with age are small for both finger BMD and trabecular density of the radius by pQCT [9]. Radius BMD declines more slowly than axial BMD until age 65, when axial loss, at least spine loss, slows.

The decrease of forearm BMD with age leads to a decrease of T-scores that is relatively comparable with different densitometers, and fairly similar at distal and proximal sites (Figure 1). Some clinicians naively believe that loss of trabecular bone at the distal radius is more rapid and hence that site could be more "diagnostic." In fact, purely trabecular bone, determined by pQCT, decreases with age at only a modest rate [9]. The pattern of bone loss from the axial skeleton (spine and femur BMD) does differ dramatically from finger BMD and trabecular density of the radius (Figure 2). **Because forearm and finger BMD decline only slightly before age 70, these sites are not useful for population "screening."** British researchers [10] found that a high BMD at the distal radius (T-score above -0.8) did have value in identifying a group that had normal BMD at the spine and femur, but low radius BMD simply identified older subjects, not those at high risk of fracture. Forearm BMD continues to decline after age 65 so a low forearm BMD will "identify" many fracture cases in a group of mixed age simply because the low BMD cases are older. In older subjects (>65 years) finger/forearm and

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Forearm BMD *from page 23*

spine BMD are the least sensitive sites for assessing risk of hip fracture, while in women under 65 years finger and forearm are the least sensitive sites in relation to vertebral fracture. **In an oral presentation at the ASBMR, French researchers [11] showed that forearm BMD was not sensitive enough to use as a screening tool in women aged 45 to 60 years**. In fact, body weight (<60 kg) has been shown to indicate risk of osteoporotic fracture almost as accurately as radius BMD.

The use of forearm BMD is particularly inappropriate for screening in the immediate postmenopausal period, because the T-scores remain elevated until age 60 years (Figure 1). Unlike finger BMD and trabecular density of the radius, where T-scores remain elevated even in old age, forearm BMD declines rapidly after age 65 so that T-scores in the elderly are lower than those for axial BMD. **Forearm BMD under-estimates the prevalence of "osteoporosis" in women 50 to 59 and overestimates it in women over age 70 (Table 2).** In women, the prevalence of low forearm BMD was 2.5X greater than low axial BMD. Basing intervention decisions on forearm BMD results in treating at least twice as many patients as those who really are at high risk of fracture.

Forearm BMD, unlike os calcis BMD, is unresponsive to therapeutic interventions. At best, there are only small changes of forearm BMD in response to alendronate over several years (1% for forearm, 2% total body, 3 to 4% at femur, and 5 to 9% spine) [16]. In all studies with antiresorptive agents (calcitonin, SERMs, estrogens, bisphosphonates), the small forearm response, if any, correlated poorly, if at all, with increases at axial sites, and with some agents (fluoride, PTH) the forearm may decline significantly even when spine BMD is increased. This creates a diagnostic "conflict" when patients previously treated with bisphosphonates are researched, since they will remain "osteoporotic" even though their axial BMD has been normalized.

Table 2. T-scores for forearm and spine BMD and percent of women below -2.5 SD. Before age 60 forearm "underdiagnoses" and after age 70 forearm BMD "overdiagnoses."

	FOREARM BMD		SPINE BMD		FOREARM
AGE	T-Score	%<-2.5 SD	T-Score	%<-2.5	% Spine
50-59	-0.4	2	-0.9	7	28%
60-69	-1.5	17	-1.7	23	74%
70-79	-2.4	50	-2.0	33	152%

Patel et al [12] compared the forearm T-score with that for the spine and femur neck BMD. The forearm T-scores in the patients referred for testing were 0.4 to 0.7 SD lower at axial sites up to 60 years, but after age 60, the forearm declined. In this same study, the distal forearm values supplied with the DTX-200 were incorrect, and even differed from the normal values reported by the manufacturer [13]. The reference values supplied with forearm pQCT devices also have been questioned [9].

Melton et al [15] recently demonstrated that the prevalence of abnormality using forearm BMD was 9X higher than spine BMD and 2X that of femur neck BMD in men. In

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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
	SERMs	Anabolic Steroids
	Bisphosphonates	PTH

Update: Estrogen

Estrogen continues to be one of the most widely used drugs in post-menopausal women, but the typical treatment is for menopausal symptoms and may last less than one year. Long-term estrogen replacement therapy (ERT) for prevention of osteoporosis (or for other indications such as heart disease) is rare despite many positive observational studies amassed over the last 20 years. Estrogen also may prevent loss of cognitive ability, and may have some protective effect against osteoarthritis. There are possible side-effects of long-term ERT, including increased risk of stroke, thrombosis, and cancer [1-4]. The recent review by Colditz et al [5] assessed the possible relation between estrogen and risk of breast cancer. The 30 to 50% increased risk of breast cancer associated with ERT is considered within the realm of error by gynecologists, given several studies showing little increased risk. The risk of ERT in patients with high BMD and/or a family history of cancer may be higher. **Even without ERT, high BMD increases risk of breast cancer 50% in women without family history and 300% in women with family history [6].** Long-term ERT may involve higher risks in these and other groups, and physicians should discuss the risks and benefits with their patients [7,8].

Ideally long-term ERT should be targeted at those women with high fracture risk, elevated cholesterol, and low-risk of breast cancer. **A low BMD value, which indicates a high risk of osteoporosis, is useful not only in targeting ERT to women who most need fracture prevention, but to those women who also have elevated cholesterol and low risk of breast cancer.** High BMD coupled with a family history of breast cancer may contra-indicate ERT and could suggest the need for SERM treatment.

There is substantial evidence for a protective effect of estrogen on bone turnover, bone density, and fracture [8-10], and evidence continues to accumulate showing the patient groups in which efficacy is clearest. Michaelson et al [12] showed that there was little significant fracture protection of ERT in physically-active women with higher body weight. They concluded that *"there seems to be only a small added benefit for hip-fracture protection in women with high physical activity or among those weighing over 70 kg."* The latter group typically has higher BMD levels. **Physicians should consider inactive women with low body weight especially in need of long-term ERT.**

ERT, like all antiresorptives, needs to be given long-term, for once therapy stops bone loss accelerates; there is no residual effect 5 years post-discontinuation. New studies show that even low estradiol levels are protective of bone in post-menopausal women [13,14]. Perhaps women who choose to terminate ERT after several years can be protected long-term with isoflavones, or other compounds with low estrogenic activity [15,16].

The evidence for a protective effect of ERT on heart disease has seemed positive, since estrogen reduces cholesterol and improves both vasculature and blood flow [17-23]. **Many observational studies, and meta-analyses, have demonstrated a 30% reduction in heart disease.** A new study has raised questions [24]. Hully et al [25] studied 2763 women with coronary disease in the HERS study, and found that estrogen did not decrease myocardial infarction or death rates, even though the expected lipid changes did occur. This prospective study contrasts with many observational trials. Importantly this study was undertaken in women with existing coronary disease who probably had risk factors that were not modifiable by estrogen. **The reasonable conclusion is that long-term ERT should be targeted at women with high risk of heart disease [26,27], but its cardioprotective benefit in those with established disease remains unproven.**

A recent review by Elizabeth Barrett-Connor concluded that definitive data on the risk-benefit of ERT were not yet available, and that therapy probably should be delayed until after age 60 [28]. Virtually all gynecologists, and many other osteoporosis specialists, would find this much too conservative an approach. **The common ground may be to target long-term ERT to patients with the greatest risk of both osteoporosis and heart disease, and with the lowest risk of side-effects.**

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Estrogen *from page 25*

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Update: Calcitonin

Calcitonin has been used for the past 15 years in the prevention and treatment of osteoporosis [1], although the first use was to reduce osteoclastic activity in Paget's disease. The approval of the nasal spray formulation in many countries has made long-term compliance possible. A dose of 100 to 200 IU/day increases spine BMD by about 1 to 2%/year, comparable to the increase observed with SERMs [1]. Long-term studies (5-years) using nasal calcitonin were reported at recent meetings [2,3]. Patients treated with 200 IU/day showed a 35 to 40% reduction in vertebral fracture, while those treated with 100 and 400 IU/day showed a 20% reduction.

Injectable calcitonin was used a decade ago in relation to the bone loss of immobilization. More recently Cepollaro et al [4] showed that calcitonin increased Stiffness of the os calcis significantly in Sudeck's atrophy of the foot. An earlier study also had shown a positive effect of calcitonin on os calcis Stiffness in osteoporotic patients [5].

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Update: Bisphosphonates

Bisphosphonates have become well-accepted drugs for treating osteoporosis in patients over 65 years with high fracture risk [1,2], although estrogen remains the preferred drug in the immediate postmenopausal decade because of its positive effects on menopausal symptoms. The results from the EPIC study in women 45-59 years of age showed that alendronate (Fosamax® by Merck) at only 5 mg/day increased spine BMD by 3.8% over four years; estrogen increased it 5.2 to 7.6% or about what would be expected with 20 mg/day of alendronate in younger women [3,4]. Most older high-risk patients will not take estrogen and should receive a bisphosphonate, but even those with osteoporotic fractures are rarely prescribed any drug by general practitioners.

The recent meetings of the Intern. Osteoporosis Foundation in Berlin and the ASBMR/IBMS had numerous reports on bisphosphonates, many of which confirmed positive effects on both axial bone density and fracture in both men and women [5-12]. The increase of axial BMD produced by alendronate was proportional to its anti-fracture efficacy [8].

The increase of BMD values in trabecular areas (spine, trochanter, os calcis) observed after bisphosphonate treatment is due only in part to a greater volume of bone. Trabecular bone volume measured on iliac crest biopsy is too variable to directly examine possible bone increases [13-15]. Bisphosphonates decrease osteoid volume and bone turnover markedly, suggesting that the observed BMD increase may be due in part to increased mineralization (Table 1). **Mineralization of trabecular areas typically is 62%, and could be increased to the 67% level of compact bone by decreasing turnover (thereby producing up to an 8% increase of BMD) [15].**

Table 1. Histomorphometry in alendronate-treated women after 36 months [13].

	Placebo	5 mg	10 mg	20/5 mg
Trabecular Bone Volume (%)	14.7	14.3	16.6	12.5
Osteoid Volume (%)	1.12	0.46	0.12	0.27
Activation Frequency	0.45	0.22	0.04	0.08

Alendronate halves the rate of vertebral and hip fractures in women with pre-existing fracture, and reduces the rate of clinical fractures by 18 to 36% (Table 2). Alendronate even decreases turnover, and increases axial BMD, in patients who fail to respond to etidronate [16]. While cyclical etidronate treatment is well-tolerated, about 20 to 30% of patients simply fail to respond with BMD increases. These overall positive results with alendronate in women with pre-existing fractures are more limited in women without fracture.

Table 2. Rate of incident clinical fracture (spine and non-spine) in women (55 to 81 years) with femur neck BMD below average (T-score <-1.6 SD). Women with prevalent vertebral fractures reported by Ensrud et al [2] and women without (w/o) prevalent vertebral fractures reported by Cummings et al [17].

T-SCORE	FRACTURE RATE (%) OVER 4 YEARS: PLACEBO	ALENDRONATE	Δ	RELATIVE RISK	FRACTURE REDUCTION
<-2.2 with FX	21.3	15.2	6.1	0.69	-31%
<-2.5 w/o FX	19.6	13.1	6.5	0.64	-36%
>-2.2 with FX	13.3	11.3	2.0	0.82	-18%
>-2.5 w/o FX	10.9	11.8	-0.9	1.08	+8%*
Overall with FX	18.2	13.6	4.6	0.72	28%
Overall w/o FX	14.1	12.3	1.8	0.86	-14%*

*Not significant

A major arm of the Fracture Intervention Trial now has demonstrated that alendronate for 4 years significantly reduced the incidence of clinical fractures in women with a femur neck T-score below -2.5 SD [17]. About 4272 women completed the trial for which low BMD (femur neck T-score <-1.6 SD and no prevalent fracture) were the entrance criteria. Over the 4 years, femur BMD increased by 3 to 4%, and spine BMD by 8% over baseline, in treated patients. There was a non-significant (p=0.07) 14% reduction in the rate of clinical fracture in the overall sample (Table 2). **It is noteworthy that there was a significant 36% reduction in the rate of clinical fracture in women with femur neck BMD <-2.5 SD. The rate for morphometric spine fracture was halved in women with "osteoporosis" at the femur neck.**

Bisphosphonates also are preferred for prevention of the bone loss secondary to use of oral corticosteroids [18-22], and should reduce the high fracture rate in this patient group. The increase of axial BMD with bisphosphonates over one or two years in corticosteroid-treated patients is about half that seen in osteoporotic women. **Bisphosphonates are especially useful for (a) patients who have both low femur density (<-1.5 SD) and prevalent fracture, (b) those with a femur neck T-score <-2.5 SD, and/or (c) those receiving high-dose oral corticosteroids.** The failure of the clinical trials of etidronate in the US to show fracture efficacy may be due to the inclusion of women without fracture who had BMD above -2.5 SD; studies of etidronate in high-risk women show that it is effective [7].

For bisphosphonate therapy to be cost-effective, it must be continued to be taken properly long-term, a challenge with any chronic therapy. Unfortunately, compliance with recommended rules for safety and efficacy of alendronate administration has been poor [23]. Some early termination in clinical practice has been associated with gastrointestinal complaints [23], which contrasts sharply with the virtual absence of complaints in controlled clinical trials where patient education is good, compliance is high and a control group is used.

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Bisphosphonates are known to cause gastrointestinal problems, and this may be exacerbated at low pH [24]. A study from Kaiser Permanente showed that only 1 in 8 patients (12%) receiving oral alendronate developed mild gastrointestinal problems [25]. Complications doubled for alendronate-treated patients over age 70, and tripled for those with a prior history of gastric problems. **This modest side-effect profile must be considered in light of the fact that alendronate halves the rate of fractures in high-risk subjects.** The Kaiser Permanente results imply that one alendronate-treated patient would develop mild gastritis for every clinical fracture prevented; experienced physicians feel this side-effect profile is acceptable, and can be improved by better patient education.

Discontinuation of bisphosphonate therapy leads to acceleration of bone loss which is similar to the rapid bone loss that occurs after estrogen or SERMs are discontinued. Wasnich et al [9] showed that bone loss resumed after subjects terminated treatment with low-dose (2.5 or 5 mg/day) alendronate. Spinal, femoral, and total body bone loss was about 1% per year post-discontinuation. Loss after discontinuation of high-dose (20 mg/day) alendronate may be slower [4]. The loss rate was even higher, 2% per year, after withdrawal of ibandronate [26]. There was no residual effect of bisphosphonate treatment on bone 5 years after discontinuation. Since 90% of patients in clinical practice discontinue chronic therapies, including bisphosphonate therapy, within two years, alternative dosage forms need to be considered that allow treatment to be continued long-term.

Researchers are seeking solutions for better compliance, including the use of cyclical alendronate (one month on followed by one month off), or interval treatment with higher doses, such as 40 mg, once or twice per week [27,28]. Merck is conducting a clinical trial of weekly therapy with 35 and 70 mg tablets. If this weekly treatment is effective, then the annual cost of drug could be halved, side-effects minimized, and compliance increased. Another approach is to use bisphosphonates with high potency yet low irritability, such as zolendronate (Novartis) and ibandronate (Roche) [29,30]. Oral agents could be given intermittently (once/month, for example) and still be quite potent. The projected mode for ibandronate is injection once every three months; this should provide a needed improvement to long-term compliance.

Recent reports showed that risedronate (P&G), another bisphosphonate nearing FDA approval, produced significant increases in spine and femur BMD, but not radius BMD at doses of 2.5 and 5.0 mg/day [9,30]. Risedronate was also effective in corticosteroid osteoporosis [31-35]. The skeletal effects of risedronate were quite similar to those produced by comparable doses of alendronate. In contrast, Genant et al [36] showed that tiludronate (Sanofi) treatment was no better than placebo; tiludronate increased spine BMD by <1% compared to placebo over 36 months, and there was no decrease in fracture rate. **It appears that tiludronate has no significant effect on either BMD or fracture.**

Pamidronate is an aminobisphosphonate that has potent antiresorptive properties; it usually is given intravenously to avoid gastrointestinal irritation. Intravenous pamidronate (Aredia7 by Novartis) is commonly used in hypercalcemia of malignancy, but also is effective in osteoporosis. A single 90 mg infusion prevented corticosteroid bone loss for 1 year [37]. Enteric-coated oral capsules of pamidronate appear to be well-tolerated, and apparently the dose is adequately absorbed since the drug is effective [10,11]. Other oral aminobisphosphonates potentially could be encapsulated for better safety and compliance.

New studies are being done using **bisphosphonates in combination with other agents**. There appears to be only a small incremental effect of estrogen and alendronate [38,39], but calcitriol doubles the BMD increase produced by bisphosphonates alone [40,41].

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Update: Vitamin D

Vitamin D, and the active forms of D-hormone, are increasingly investigated because of their multiplicity of genomic and possible non-genomic actions. Receptors are present not only in bone and intestine, but in many other tissues [1-3]. The conventional viewpoint is that there is little or no vitamin D deficiency in western societies, perhaps because healthy, ambulatory older subjects with normal bone mineral density (BMD) rarely have either low calcidiol levels or elevated PTH [4]. **A number of studies have shown that subclinical D deficiency is present in a significant minority of the elderly at least seasonally in higher latitudes [5-15]**. Even in relatively sunny climates, like Spain, low calcidiol levels (<15 ng/ml) occurred in 60% of younger post-menopausal women [16]. Some of these differences may be due to analytic differences in calcidiol determination; **there is a need for standardization of calcidiol analyses**. Other differences may simply reflect the absence of vitamin D food fortification in many areas. Frank deficiency is sometimes thought to occur only when the calcidiol level is very low (<12 ng/ml), but in the elderly, hypovitaminosis may occur at higher levels [7-9]. **PTH levels increase rapidly in the elderly at calcidiol levels <30 ng/ml compared to <15 ng/ml in young individuals. If this is confirmed, hypovitaminosis in the elderly could conceivably be defined as calcidiol <20 ng/ml.**

Vitamin D status is particularly compromised in the non-ambulatory elderly, particularly those in institutional care [10-13]. A controversial report in the *New England Journal of Medicine* [17] showed that hypovitaminosis also was common in the general medical population. A recent publication confirmed that over 70% of critically-ill patients had calcidiol levels under 20 ng/ml, and 42% had elevated PTH [18]. A low calcidiol in non-ambulatory subjects is of particular concern because bone loss is doubled in D-deficient subjects who are immobilized [19]. Krieg et al [12] found that over 50% of institutionalized subjects had calcidiol levels below 10 ng/ml. Calcidiol levels are twice this level in the ambulatory elderly [4,12].

Calcidiol levels are particularly low in patients with hip fracture [20-22]. **One of the key factors in fracture may be myopathy associated with D-deficiency, along with an increased body sway, and increased risk of falling [23,24]**. Several studies also have suggested that the vitamin D receptor may be associated with risk of fracture [25]. Patients with fracture do show a particular defect in calcium absorption [26,27]. A defect of calcium absorption in the aged is often associated with intestinal “resistance” to 1,25-D_3 and not just low calcidiol or calcitriol levels [28,29], but it is unclear if vitamin D receptor status is associated with this resistance. **The mild secondary hyperparathyroidism that occurs in elderly patients can be corrected in part by low-cost vitamin D supplementation (800 to 2000 IU/ day or 50,000 to 100,000 IU once per month); a less effective and more costly alternative is supplementation with high-dose calcium [30-34]**. Calcium alone (intakes under 1000 mg/day) has no suppressive effect on PTH [35], and would not improve the muscle weakness of D-deficient subjects. A German research group that initially showed that vitamin D is related to body sway and falls [24], reported at the ASBMR that a small (800 IU/day) supplement of vitamin D improved balance and body sway [36]. In contrast, 1200 mg/day of calcium had no effect on sway [36]. **Compston [37] has pointed out that the evidence now supports routine supplementation of the elderly with a daily dose of 800 IU (20 μg). She noted “this dose is safe, free of side effects, and should have an impact on the enormous and increasing morbidity and cost attributable to osteoporotic fracture in elderly people.”** It is doubtful if there is any value in special (>400 IU) vitamin D supplementation of normal subjects under age 60, since deficiency at this age is extremely rare. Finnish researchers [38] showed that the addition of 300 IU to estrogen therapy had no effect on spine BMD. The supplement increased the response of femur BMD to estrogen, but the 50% fracture reduction with vitamin D alone was not significant in this five-year study because of the small sample size [38].

Correction of elevated PTH by vitamin D supplementation may not address all skeletal problems, particularly the defective calcium absorption. Active D-hormone, or a “pro-drug,” may be needed in many elderly patients [39,40]. Active hormone has a direct effect on osteoblasts [41-43]. Both alphacalcidol and calcitriol have been used extensively throughout Asia and Australia, and even in certain European countries, over the last several years with success in treating osteoporosis. This effect on osteoblasts may be important, particularly in corticosteroid-induced osteoporosis where bone formation is compromised. Low-dose therapy (0.5 μg/day calcitriol, or 1.0 μg/day alphacalcidiol) increases spine and femur BMD in patients treated with low-dose prednisone (<8 mg/day) [44]. Bisphosphonates are preferred for treating corticosteroid osteoporosis, but could be combined with active D-hormone for better efficacy.

At the European Congress of Osteoporosis in Berlin, many papers showed that alphacalcidol and calcitriol were both effective in treating osteoporosis [45-51]. Alphacalcidol seems preferred by many clinicians because this pro-drug has a wider therapeutic window than calcitriol itself, and the pro-drug provides sustained elevation of 1,25-D_3 levels in bone and in blood, with less “first-pass effect” on gut compared to calcitriol.

One interesting emerging therapeutic alternative is adjuvant therapy with calcitriol or alphacalcidol. Combined therapy of estrogen with bisphosphonates offers no skeletal advantage beyond that of bisphosphonate alone, but an active D-hormone combined with either estrogen or bisphosphonate greatly accentuates the BMD increase of either antiresorptive and further decreases fracture rate [52-54].

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ORCA-DX™: Fluoroscopic Densitometry

The ORCA is a portable C-arm designed for extremity fluoroscopy during surgery on the limbs. It utilizes a 6” (15 cm) image intensifier coupled to a high-capacity x-ray generator, both of which are mounted on a versatile C-arm. An optional densitometry application (ORCA-DX) has been developed for measuring BMD of the os calcis or forearm using dual-energy x-ray absorptiometry (DEXA). Measurements are taken at 50 and 75 kVp over 3 seconds; the DEXA data are analyzed by a conventional computer, and results, including T-score, Z-score, and fracture risk, are printed out. The $12,000 “DX” option for the ORCA includes a separate limb-positioning device, a computer and printer, and densitometry software. The BMD results have been shown to correlate highly (r>0.98) with those obtained at the same site on the PIXI and DPX densitometers. Precision *in vivo* is 1%, and the exposure radiation dose to the limbs is under 10 mrem.

FDA approval of raloxifene (Evista™ by Lilly) in the USA last year for prevention of bone loss has led to increased credibility that selective estrogen receptor modulators (SERM), or antiestrogens, could be useful for postmenopausal women [1-5]. Surprisingly, financial analysts report that sales of Evista have been below expectations.

Tamoxifen has long been used as an adjuvant to prevent recurrence of breast cancer [5-7], but it has been ineffective in the long-term maintenance of bone and prevention of fracture. Tamoxifen received FDA approval recently to prevent breast cancer in high-risk women based on short-term studies in the US. Long-term European studies, however, failed to show protection against breast cancer. Exciting findings on raloxifene were presented at the Annual Breast Cancer Symposium this December 1998 in San Antonio; **short-term treatment (40-months so far) prevented breast cancer (reportedly a 75% reduction in estrogen-receptor positive tumors, and a 55% reduction in all breast cancers).** Raloxifene could gain approval for breast cancer prevention in the US, although long-term studies now seem mandatory to assess efficacy. What is most remarkable about the protective effect of raloxifene is that risk was reduced in women with low axial BMD, a group that already has low risk of cancer.

Raloxifene, like tamoxifen, produces only small increases of axial BMD (only 1 to 2% above baseline over 2 years) [8,9]. In fact, a recent study from the Mayo Clinic showed no significant bone increases after 12 months of treatment at either 60 mg/day or 120 mg/day [10]. Raloxifene produces no adverse effects on mineralization, but likewise no increase in trabecular bone volume [11]. Several studies have demonstrated that raloxifene decreases bone turnover only half as much as potent bisphosphonates. **Recent reports on the MORE study, a large trial in 7700 women with low BMD or fracture, also showed no significant reduction of clinical fractures (only 3 to 9%) even though there was a 50% reduction of morphometric (non-clinical) vertebral fractures [12,13]. In contrast, alendronate produces a 36% reduction of clinical fractures in similar high-risk women.**

Raloxifene, like tamoxifen, decreases lipid levels [14] but this may not translate directly into less atherosclerosis. Raloxifene might protect against coronary disease, but this remains unproven. Bjarnason et al [15] found that raloxifene inhibited aortic atherosclerosis in rabbits, but Clarkson et al [16] found that raloxifene had no effect on atherosclerosis in monkeys even though it lowered lipid levels slightly; in contrast, estrogen prevented atherosclerosis. The claims of "estrogen-like" protective effects are also becoming uncertain as both retrospective and prospective studies now suggest that homocysteine reduction is a key element in reducing the risk of both myocardial infarction and stroke. **The conventional dose of raloxifene (60 mg/day) does not reduce plasma homocysteine levels, but conjugated estrogen does [17].** High-dose raloxifene (150 mg/day) is needed to reduce homocysteine; chronic tamoxifen treatment of women with breast cancer does reduce homocysteine levels. Of course **a multi-vitamin is a much cheaper and safer means of reducing homocysteine levels.**

Other SERMs, like droloxifene, levormeloxifene, and idoxifene, have modest skeletal effects in experimental animals [18-20], and postmenopausal women [21]. More potent SERM analogs, perhaps in combination with vitamin D-hormone, offer promise of a more significant skeletal effect, yet with the positive side-effect profile.

Continuation of the raloxifene fracture trials long-term should be able to better show if this promising agent has any significant effect on clinical fractures, particularly costly hip fractures. These long-term studies also will clarify the protective effect in relation to breast cancer. Until then, many physicians probably will choose to treat osteoporosis with agents proven to prevent clinical fractures, and use raloxifene only in women with high risk of breast cancer.

A major new trial (Study of Tamoxifen and Raloxifene, or STAR) will start this year; 22,000 women at high risk of breast cancer will receive either of the two agents [22]. This could better demonstrate the clinical effects of both agents.

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Update: Fluoride

Fluoride was once considered a useful treatment for osteoporosis in the United States, and it is still utilized in Europe. **Fluoride clearly stimulates bone cells and produces an increase in the density of trabecular bone [1-3]**. However, the therapeutic window may be narrow, and at higher levels the increased porosity of compact bone can diminish bone strength and increase risk of fracture. Long-term exposure at low doses does not have the adverse effects seen at higher-doses. Water fluoridation is not associated with an increased risk of hip fracture [4]. Long-term exposure through water systems can have a positive impact on axial BMD, although fluoride levels must be somewhat higher than the low levels used to prevent dental carries (0.7 to ~1 mg/l) [5].

The data on fracture prevention with fluoride treatment have been equivocal, probably because some studies have used higher doses of immediate-release formulations that are clearly problematic [6-8]. Still fluoride therapy does produce a large increase of spine BMD, even though it has little effect on compact bone [7-10]. **In this regard, fluoride is much like parathyroid hormone, or perhaps even superior; 1-84 PTH injections produce large increases of spine BMD over one year, but no increase of femur BMD, and a profound decrease (2%) of total body BMC [11]. The two anabolic agents should be viewed similarly, and both must be questioned until conclusive evidence is available to show that they do not have adverse long-term effects.** The major deficiency of fluoride may be that it is not backed by a multi-national pharmaceutical company with the funding needed for long-term trials and massive marketing campaigns.

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Current Readings

The following index is organized by topic. The numerical notations correspond to the alphabetical listing of authors that begins on page 37. LUNAR does not supply copies of the articles listed in this index. **The number following the page numbers is the Unique Identifier (UI). This UI number can be used to access the article or abstract at the following internet site: http://www.ncbi.nlm.nih.gov/PubMed**

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Upcoming Meetings – 1999

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

- March 7-12, **European Congress of Radiology**, Vienna, Austria. Contact: ECR-Office, Neutorgasse 9/ 2A, A-1010 Vienna, Austria Tel +43 1 533 40 64; Fax: +43 1 533 40 649; website www.ecr.org.
- March 28-April 2, **Third International Conference on Osteoporosis**, Xo'an, China. Contact: Prof. Dr. Zhonghou Liu, No 38, Hui Xin Li, Chao Yang District. Beijing. 100029, P.R. China. Tel: 0086-10-64976420, 64985881; Fax: 86-10-64976421; E-mail: CGSOC@hns.cjfh.ac.cn.
- April 29-30, **International Federation of Societies on Skeletal Diseases,** Buenos Aires, Argentina. Contact : O.D. Messina, JE Uriburu 1170, 1st Floor - Apt B, Buenos Aires, 1114, Argentina. Tel: 54-1-822-7230; Fax: 54-1-822-7230.
- April 22-25, **American College of Physicians,** New Orleans, Louisiana, USA. Contact: R0460 Annual Session Registration, PO Box 7777, Philadelphia, PA 19175-0460 USA; Tel:(800)523-1546, ext. 2600 or (215)351-2600; Fax: (215)351-2799. Internet: http://www.acponline.org/cme/as/1999/reg_form.htm.
- April 28-May 2, **American Association of Clinical Endocrinologists,** San Diego, CA, USA. Contact: AACE, 1000 Riverside Ave, Suite 205, Jacksonville, Florida, USA. Tel: (904)353-7878; Fax: (904)353-8185.
- May 4-7, **International Conference on Children's Bone Health**, Maastricht, The Netherlands. Contact: Leids Congres Bureau B.V., Thea van Wijk, P.O. Box 16065, 23-1 GB Leiden, The Netherlands. Tel: +31-71-514-8203; Fax: +31 71 512-8095; E-mail: lcb@pi.net.
- May 7-11, **European Symposium on Calcified Tissues**, Maastricht, The Netherlands.. Contact: Leids Congres Bureau B.V., Thea van Wijk, Box 16065, 2301 GB Leiden, The Netherlands. Tel: +31 71 514 8203; Fax: +31 71 512-8095; E-mail: lcb@pi.net.
- May 9-14, **American Roentgen Ray Society** New Orleans, LA, USA. Contact: ARRS, Leesburg, VA. Tel: (703)729-3353; Fax: (703)729-4839.
- May 15-19, **American College of Obstetrics and Gynecology**, Philadelphia, PA, USA. Contact: ACOG, 409 12th St., S.W., PO Box 96920, Washington, D.C. 20090-6920; E-mail to: Mark Graves mgraves@acog.org; Internet: http://www.acog.org.
- July 1-4, **Mediterranean Conference on New Strategies in Diagnosis and Treatment of Osteoporosis**, St. George's Bay, Malta, Contact: Organizing Secretariat, Regia Congressi, Via II Prato, 11/r, 50123 Firenze, Italy. Tel: +39 55 27761; Fax: +39 55 277180.
- August 4-7, **Portland Bone Symposium**, Portland, Oregon, USA. Contact: Symposium Administration, Oregon Health Sciences University. Tel: (503)494-1322; Fax: (503)494-8378; E-mail pbs@ohsu.edu or register online at http://www.ohsu.edu.nhwc.
- September 23-26, **Polish Osteoarthrology Society and Polish Foundation of Osteoporosis**, Cracow, Poland. Contact: Professor Edward Czerwinski, X Symposium Organizing Committee, ul. Kopernika 19c, 31-501 Krakow, Poland. Tel: (4812)618-88221; Fax: (4812) 618-8827.
- September 23-25, **North American Menopause Society** New York, NY USA. Contact: NAMS, Cleveland, Ohio. Tel: (216)844-8748; Fax: (216)844-8708.
- September 30-Oct 4, **ASBMR**, St Louis, MO, USA. Contact: ASBMR Office, 1200 19th Street, NW, Suite 300, Washington, DC 20036 USA. Tel: (202)857-1161; Fax: (202)223-4579; E-mail: asbmr@sba.com.

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