Dual-Energy X-ray Absorptiometry: A Precise Method of Measuring Bone Mineral Density in the Lumbar Spine

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We compared two methods of measuring spinal bone mineral content and density (BMC/BMD): conventional dual-photon absorptiometry (DPA) and a more recent method, dual-energy x-ray absorptiometry (DEXA). The clinical usefulness of both methods was compared in the measurement of BMC in the forearm. DEXA had a long-term in vivo precision of 1% which was significantly better than that of DPA. Changes in the distribution of fatty tissue influenced the accuracy of the two spinal methods in different ways. Forearm BMC discriminated between the bone mass of early and late postmenopausal women to the same degree as DPA and DEXA. The variability in the response to estrogen treatment and placebo was much lower with DEXA and forearm BMC than with DPA. We conclude that DEXA provides a fast and precise measurement of spinal BMC/BMD. The accuracy remains to be evaluated for in vivo studies.

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Determination of bone mineral content (BMC) and bone mineral density (BMD) has become essential in the investigation of the calcium metabolism and in associated diseases. BMD is defined as BMC divided by the area of interest, g/cm^2. It has been intensely debated in which part of the skeleton the bone mass should be determined. The vertebral body consists mainly of trabecular bone, which seems to be more affected in several metabolic bone diseases than does cortical bone (*1,2*). Correspondingly, osteoporotic patients often present with spinal crush fractures. Measurements of the spinal BMC and BMD have thus been advocated for diagnostic purposes (*2–4*). But the vertebrae are irregular in shape and are surrounded by a thick layer of soft tissue, the composition of which varies widely not only from one person to another, but also within the same person. For instance, the fat content in the capsules of the kidneys brings about a nonsystematic inaccuracy in the bone measurements (*5*). The spine is an inherently complicated, but clinically relevant, area of the skeleton to measure. Dual-photon absorptiometry (DPA) and quantitative computed tomography (QCT) (*1*) are the conventional methods of measuring spinal BMC and BMD.

The forearm, which consists mainly of cortical bone, is regular in shape and surrounded by only a thin layer of soft tissue. It is, therefore, a relatively uncomplicated area in which to measure the BMC. But several studies have reported that forearm BMC is not a reliable estimate of either the BMC or the BMD of the spine (*6,7*). Determination of forearm BMC, normally performed by single-photon absorptiometry (SPA), is, therefore, considered to have less clinical relevance than spinal measurements.

Unlike forearm SPA measurements, spinal DPA measurements have proved too imprecise for follow-up measurements unless very large groups of subjects are studied (*8–10*). Recently, a new technique for measuring spinal BMD, dual-energy x-ray absorptiometry (DEXA), has been reported to have a high short-term in vivo and long-term in vitro precision (*11–14*). We tested this technique, including the long-term in vivo precision, and applied it in a clinical, controlled trial. DEXA was also compared with spinal DPA and SPA of the forearm.

MATERIALS AND METHODS

DEXA measurements of BMD in the lumbar spine were performed with a Hologic Inc. (Waltham, MA), model QDR™-1000 bone densitometer (software version 3.10). This system uses an x-ray tube with 75 kVp and 150 kVp pulses alternately applied across it as source instead of a radioactive source. The source collimator is 2.3 mm. The scan speed is 45 mm/sec and the step size is 1 mm; the recommended length and width of a scan are 20.0 cm and 12.5 cm. One scan thus takes ~ 9 min. The QDR™-1000 employs an internal

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calibration wheel composed of materials equivalent to bone and soft tissue, as well as an empty "air" segment. These materials rotate 60 times/sec through the x-ray beam between the x-ray tube and the patient, thus providing continuous calibration on a pixel by pixel basis. Measurements in each pixel are performed for both energies with all three wheel calibration materials (bone, soft tissue, and air) interposed.

The BMC of a sample is calculated through an iterative procedure as:

$$BMC = K_1 * (K_2 * \ln I_H^{air} - \ln I_L^{air})$$

and

$$K_2 = (\ln I_L^{st} - \ln I_L^{air})/(\ln I_H^{st} - \ln I_H^{air}),$$

where I_L^{air} and I_H^{air} as well as I_L^{st} and I_H^{st} indicate low- and high-energy measurements with air and soft tissue (st) interposed by the calibration wheel. The constant K_2, which depends on the nature of the tissue composition, is determined in each patient as an average value from all pixels. The proportionality constant K_1, which converts arbitrary units into actual BMC (g), is determined by measuring the degree of shift in the measured bone value when the bone material is interposed by the calibration disk. The BMD is then calculated as BMD = BMC/area (g/cm^2).

DPA measurements of BMD in the lumbar spine were performed with a spine scanner developed in our laboratory, with a gadolinium-153 (37 GBq) source. One scan takes ~ 50 min. This scanner was validated against the commercially available DP3 spine scanner (Lunar Radiation Corporation, Madison, WI, software version 07E) (*15*) and adjusted to its measurement level.

Both the QDR and DPA systems are anterior-posterior projection techniques and calculate BMD in vertebrae L2 to L4, including the intervertebral discs. Both systems are able to retrieve the previous scan to the screen simultaneously with the current scan, thus ensuring the determination of identical areas of interest.

Forearm BMC was measured by iodine-125 SPA. The BMC is determined as the mean of six scans 4 mm apart just proximal to the site where the distance between the ulna and the radius is 8 mm. The results are corrected for fat (*16*) and given in arbitrary units. The long-term in vivo precision is 1% and the accuracy is 2%.

Linearity. Five standards consisting of one to five aluminum sheets of even thickness (2.0 mm), corresponding to a BMD range of 0.25–1.3 g/cm^2 and submerged in a 20 cm 28% (w/w) ethanol/water solution, were each measured five times by both QDR and DPA.

Influence of Fat Tissue Distribution. An aluminum tube (diameter 50 mm, wall thickness 3.0 mm, BMD = 1.13 g/cm^2) was measured on both spine scanners while submerged in ethanol/water solutions. The tube was measured with different ethanol/water solutions (0%, 21%, 44%, 80%, 100%; w/w) inside and outside the tube in three set-ups: The solution varied either in one compartment only or in both compartments simultaneously (Table 1). The experiment was repeated with three other tubes of different wall thicknesses but with the same diameter. As pure ethanol resembles fat and pure water resembles lean tissue in terms of x-ray attenuation, this experiment shows the influence of the marrow fat content and the abdominal fat percentage on the BMD measurements.

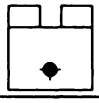
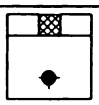
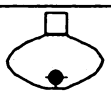
The Hologic spine phantom consists of moulded vertebrae (simulating human L1 to L4) embedded in a 17-cm high epoxy block. The R_{st} value (i.e., the ratio of the mass attenuation coefficients for soft tissue at the two energy levels) of this block, as measured by DPA, is 1.35, corresponding to a fat percentage of 81 (unpublished data).

The Hologic phantom was measured on both spine scanners without and with 2 cm of porcine lard positioned in three different ways (Fig. 1): (1) homogeneously over the whole scan

TABLE 1
Influence of Changes in Fatty Tissue Distribution in Vitro

Tube submerged in ethanol/water solution	Constant ethanol/water solution (21% (w/w))	Variable solutions (0–21–44–80–100%)	QDR	DPA
			$0.03^{NS} \pm 0.09$	$0.09^{\dagger} \pm 0.09$
			$1.04^{*} \pm 0.11$	$0.95^{*} \pm 0.06$
			$-1.08^{*} \pm 0.05$	$-0.90^{*} \pm 0.02$

An aluminum tube was measured submerged in different ethanol/water solutions.
Values are given as slopes (mg/cm^2 per ethanol %) ± 1 s.d.
* = $p < 0.01$.
†NS = not significant.

	Height	Fat %	DPA	QDR
	H	H	0.5% ± 0.2 NS	0.1% ± 0.3 NS
	I	H	-0.3% ± 0.2 NS	3.6% ± 0.2**
	I	H	-0.4% ± 0.6 NS	-3.1% ± 0.1**
	H	H	1.9% ± 0.7 NS	0.6% ± 0.1 *
	H	I	-5.7% ± 0.3 **	-6.0% ± 0.2**
	H	I	10.0% ± 0.3**	5.8% ± 0.2**
	H	H	-0.8% ± 1.1 NS	-0.3% ± 0.1 NS
	I	I	-4.0% ± 0.5 **	-1.6% ± 0.4*

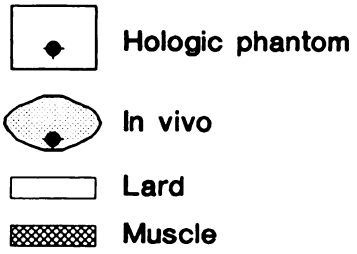


FIGURE 1
Influence of homogeneous (H) or inhomogeneous (I) absorber height and fatty tissue distribution in vitro and in vivo on QDR and DPA measurements of BMD. Values given as mean changes ±1 s.e.m. in percent of measurements without superposition of lard/muscle. * = $p < 0.05$; ** = $p < 0.001$. Height denotes the absorber thickness of the patient/phantom plus superposed materials. Fat% denotes the fatty tissue distribution in the scan area.

area; (2) inhomogeneously with the lard only lateral to the vertebrae; and (3) inhomogeneously with the lard only over the vertebrae. As lard and the epoxy block have almost the same R_{st} value (fat percentage of lard: 88, giving an R_{st} of 1.33), this experiment mainly shows the influence of different absorber heights on measured BMD values. The Hologic phantom was also measured on both spine scanners without and with 2 cm of ox muscle positioned: (1) homogeneously over the whole scan area; (2) with 2 cm ox muscle lateral to the vertebrae and 2 cm lard over the vertebrae; and (3) with 2 cm lard lateral to the vertebrae and 2 cm ox muscle over the vertebrae. This experiment illustrates the influence of inhomogeneously distributed abdominal fat on the BMD values, when the absorber height is kept constant. All measurements were performed five times. In addition to these in vitro measurements, five normal subjects (3 women and 2 men) were measured on both scanners without and with 2 cm porcine lard placed either homogeneously over the whole lumbar scan area, or with 2 cm porcine lard placed only over the vertebrae.

Lastly, QDR measurements of 30 early postmenopausal women (see below) were recalculated 6 times by gradually (steps of 1 cm) narrowing the total area of interest, i.e., by including fewer soft-tissue points in the calculations. The total area of interest was defined as the optimum symmetrical scan width obtained around vertebrae L2 to L4. The women were selected as those who had been positioned most centrally on the QDR™-1000.

Precision Evaluation. Two phantoms were used: (a) the Hologic phantom and (b) the Glostrup phantom, developed in our laboratory. The latter consists of human vertebrae (L1 to L4) embedded in a 15-cm high polyester block, which contains a small amount of plaster. The phantoms were measured on both spine scanners 10 times within a week and thereafter once a week for 6 mo. The R_{st} values of the two phantoms measured by DPA were: (a) 1.35, corresponding to a fat percentage of 81 and (b) 1.44, corresponding to a fat percentage of 28. The in vivo precision of QDR was assessed in three groups of women: (a) 10 premenopausal women aged 32 ± 6.1 yr; (b) 10 early postmenopausal women aged 50 ± 2.9 yr; and (c) 10 late postmenopausal women aged 70 ± 1.3 yr. All 30 women were measured twice, with repositioning on the same day. To assess the long-term precision, groups "a" and "b" were remeasured 6 mo later.

Clinical Application. Early postmenopausal women, aged 45–54 yr, were selected by questionnaire and medical screening. All had passed a natural menopause 6 mo to 3 yr earlier and none were suffering from any diseases nor receiving any medication known to affect calcium metabolism. These women were randomized to two groups, A (n = 59) and B (n = 57). They were then further randomized (2:1) to receive either estrogen-progestogen replacement therapy (n = 38 in group A and n = 40 in group B) or placebo therapy (n = 21 in group A and n = 17 in group B). In group A, a spinal BMD was measured by DPA initially and at 1 yr. In group B, spinal BMD was measured initially by QDR and DPA and at 1 yr by QDR. Forearm BMC was also measured initially and at 1 yr.

Twenty-three late postmenopausal women, also selected by

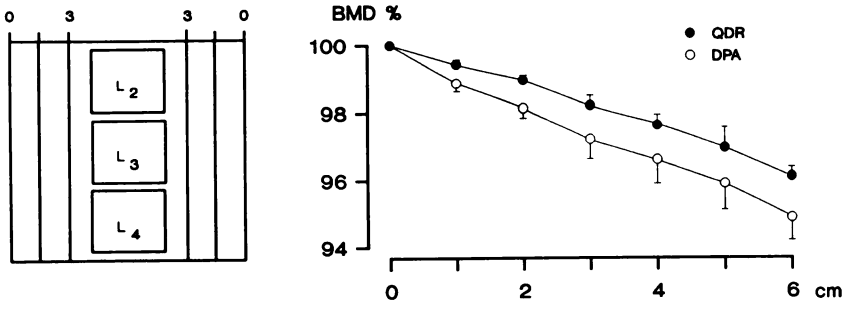


FIGURE 2
Percentage changes ±1 s.e.m. in the BMD of 30 early postmenopausal women measured by DPA (○) and QDR (●) as the total soft-tissue area of interest is narrowed by steps of 1 cm.

questionnaire and medical screening, were aged 68–72 yr and had passed a natural menopause. A single measurement of the forearm BMC and of the spinal BMD (DPA and QDR) were performed.

Calculations

The influence of homogeneous and inhomogeneous lard and muscle on BMD measurements was tested with Student's t-test for paired data. The short- and long-term in vivo reproducibilities were given as the coefficient of variation in percentage (CV%) of duplicate measurements (*8*). In the group of early postmenopausal women, the individual values were corrected for a mean spontaneous bone loss over 6 mo before calculation of the CV%. The methods were compared by linear regression analyses and the predictive error of the dependent variable was expressed as the percentage standard error of estimate (s.e.e.%).

RESULTS

Linearity. Correlation and linear regression analysis between the thicknesses of the aluminum standards and the measured BMD gave: $r = 0.99$, $y = 0.11x + 0.03$ for DPA and $r = 0.99$, $y = 0.13x + 0.001$ for QDR. The DPA intercept was significantly different from zero ($p < 0.05$), and the two slopes differed significantly from each other ($p < 0.01$). When expressed in BMC values, the regression equations were virtually equal for the two methods (DPA: $y = 10.1x - 0.5$; QDR: $y = 10.2x - 1.4$). When expressed in area values (cm^2) the regression equations gave: $y = 0.46x + 73.6$ for DPA and $y = 0.25x + 73.7$ for QDR. The two slopes differed significantly from zero and from each other ($p < 0.001$).

Influence of Fat Tissue Distribution. Table 1 gives the results of the aluminum tube experiment. The findings were similar for DPA and QDR, namely a single change in either compartment (inside or outside the tube) affected the measured BMD significantly ($p < 0.01$), whereas simultaneous changes in both compartments did not. A 100% isolated change in either compartment changed the measured BMD ~10%. Essentially, identical results were obtained with the three other tubes with different wall thicknesses. Figure 1 shows the results of the lard and muscle experiment. Homogeneously positioned lard or muscle affected neither the QDR nor the DPA measurements substantially. Inhomogeneously positioned lard on the Hologic phantom affected the QDR measurement significantly, but not the DPA measurement; inhomogeneous positioning of the lard and muscle together affected both the DPA and the QDR measurements significantly. Figure 2 shows the decrease in the BMD value obtained by DPA and QDR when the soft-tissue area of interest was narrowed.

Precision. Table 2 gives the short- and long-term in vivo and in vitro precision errors of QDR and DPA. The precision errors in vivo were uniformly higher than those in vitro; the QDR had uniformly lower precision errors than had DPA and kept its low in vivo precision error in the long term.

Clinical Evaluation. The QDR and DPA measurements of BMD were highly correlated ($r = 0.94$), but the slope of the regression differed from one ($p < 0.01$) and the intercept differed from zero ($p < 0.001$) (Fig. 3). When BMC values were used instead of BMD values we arrived at: QDR = 1.0 * DPA + 3.0, $r = 0.93$, where the slope was not significantly different from one and the intercept not significantly different from zero.

The s.e.e. from a regression between the forearm BMC and spinal BMD was higher (12% for QDR and 14% for DPA) than the s.e.e. from the regression between the QDR and DPA (s.e.e. = 6%). Short-term duplicate measurements of BMD gave s.e.e. = 1.8% for

TABLE 2
In Vitro and in Vivo Precisions of DPA and QDR: Coefficient of Variation (CV%) of Bone Mineral Density Measurements

	Short-term (within day)		Long-term (6 mo)	
	DPA	QDR	DPA	QDR
Glostrup phantom	1.0	0.5	1.1	0.9
Hologic phantom	0.5	0.5	1.4	0.3
Premenopausal women	1.2*	0.9	1.6*	0.8
Early postmenopausal women	1.8	1.2	2.1	1.1
Late postmenopausal women	2.1*	1.5	—	—

* Previously published (*15*).

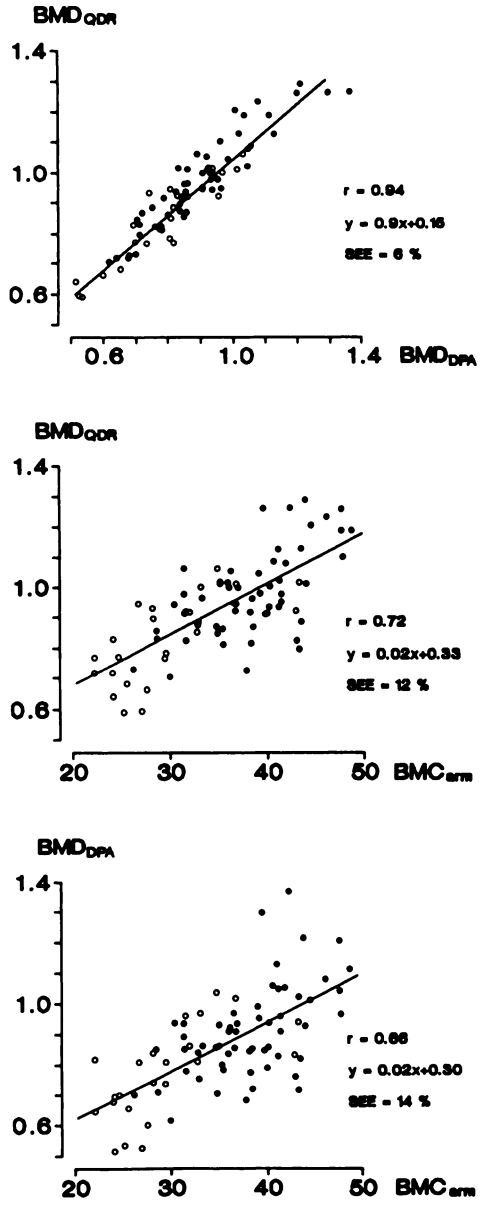


FIGURE 3
Correlations between spinal (QDR and DPA) and forearm measurements in 57 early postmenopausal women (●) and 23 late postmenopausal women (○). BMD_{QDR} and BMD_{DPA} denote BMD (g/cm^2) of the lumbar spine measured by QDR and DPA. BMC_{arm} denotes BMC (units) of the forearm measured by SPA.

a regression of QDR versus QDR and s.e.e. = 2.0% for a regression of DPA versus DPA.

Figure 4 illustrates the ability of the three methods to discriminate between the bone mass of late postmenopausal women and that of early postmenopausal women. The data are expressed as the z-scores of the early postmenopausal women. For each of the three methods, an almost equal number of 70-yr-old women had a score below −2z (QDR: 5, DPA: 7, Forearm: 11).

Figure 5 shows the individual changes in bone mass during estrogen-progestogen replacement therapy and placebo, assessed by the three techniques. The mean difference in response between the active drug group and the placebo group was approximately the same for all three measurements, but the variability was much larger for BMD measured by DPA than for BMD measured by QDR and forearm BMC.

DISCUSSION

Until recently, BMD of the lumbar spine could only be measured by DPA and QCT. Both methods have significant precision and accuracy errors (*1,8–10,17*). Marrow fat may influence QCT measurements (*1*) and the values obtained by DPA may change as a function of source life and source replacement (*8,10*). Nor is their reproducibility adequate for many clinical trials where small changes in BMD are studied.

DEXA is a new method (*11–14*). Our in vitro results showed that its linearity is as good as that of conventional DPA. The aluminum tube experiment showed that a change in fat content affects BMD measurements by both DPA and QDR, as a 10% change in marrow fat produced a 1% change in the measured BMD. The marrow fat induced inaccuracy of QCT is at least five times greater (*1*).

As expected, parallel changes in the marrow and abdominal fat percentage did not affect the BMD measured by either method. The influence of soft-tissue body composition on the measured BMD values was further assessed in the lard and muscle experiment. We found that whereas DPA only requires a similar composition of the soft tissue lateral to and above the vertebrae, QDR additionally demands a similar absorber height. Intestinal gas may thus invalidate QDR measurements and contribute to its inaccuracy.

When measuring spinal bone mass, the importance of always choosing the same "bone" area of interest is evident. Figure 2 clearly demonstrates that this also applies to the "soft-tissue" area of interest. Patients should therefore always be positioned with care.

Spinal BMD measured by QDR and DPA were highly correlated, but the regression line differed from the line of identity. This is consistent with previous findings (*11–14*). QDR and DPA thus use different units, a fact which must be kept in mind when comparing raw BMD data obtained by different instruments. The difference in the BMD measurements seems to be caused by different routines for defining the "bone" area of interest, as QDR and DPA gave similar BMC values. This is furthermore confirmed by the linearity equations when expressed in area values. The difference in the two slopes suggests a systematic difference in area determination. The error for QDR seems smaller, as its slope was closer to zero.

The fact that s.e.e.s from the regressions QDR versus QDR and DPA versus DPA were one-third of that

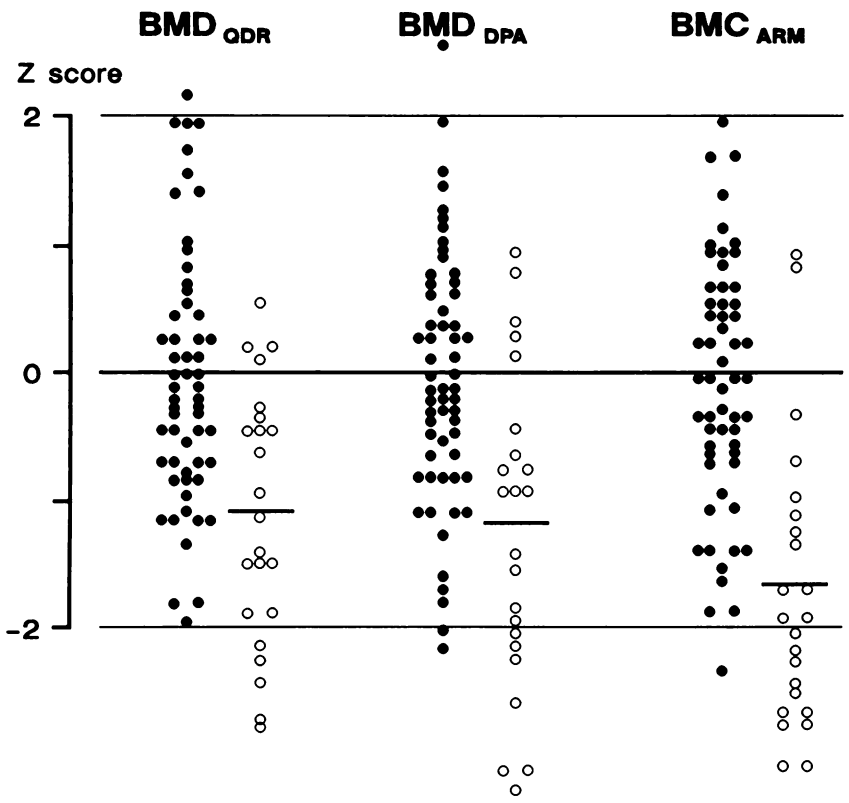


FIGURE 4
Individual values of forearm and spinal (QDR and DPA) bone mass in late postmenopausal women (○), given on a scale defined from the mean and s.d. in two equal groups of early postmenopausal women (●). BMD_{QDR} and BMD_{DPA} denote BMD of the lumbar spine measured by QDR (group B) and DPA (group A). BMC_{ARM} denotes BMC of the forearm (group B).

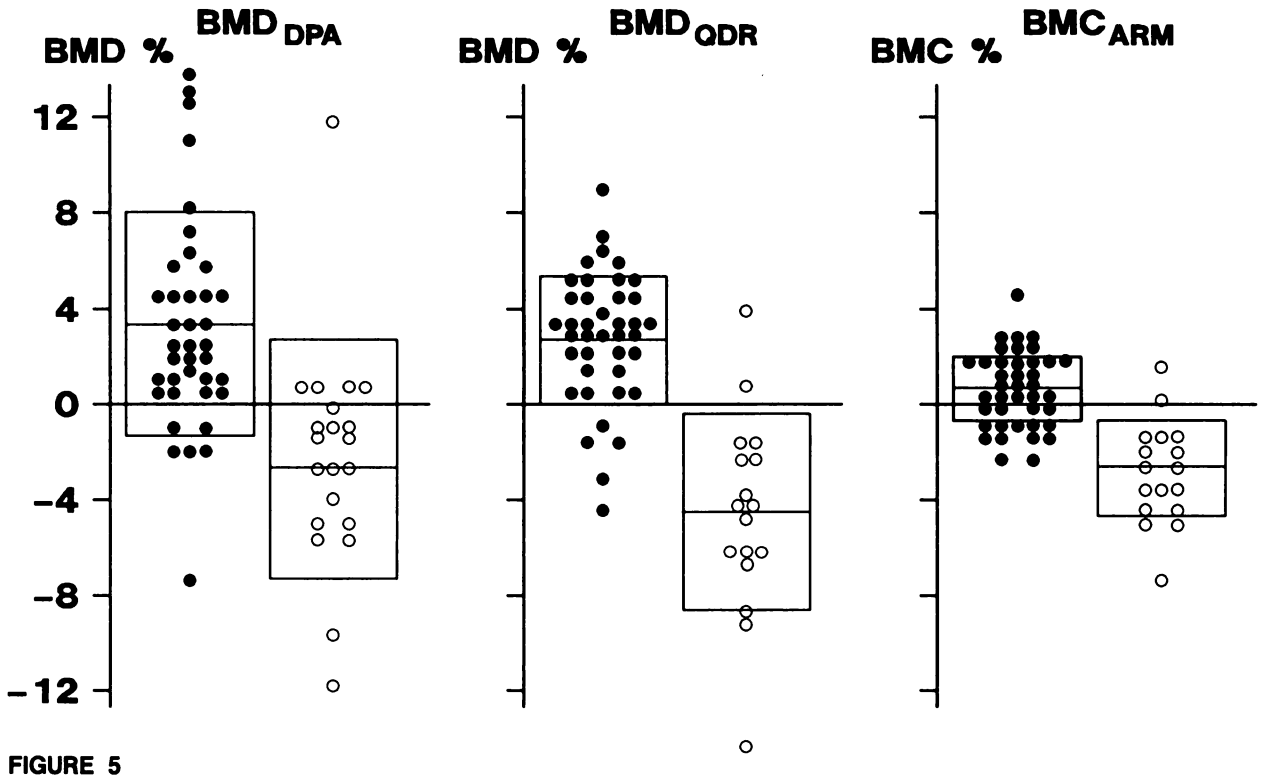


FIGURE 5
Individual percentage changes in bone mass during one year of estrogen-progestogen therapy (●) and placebo (○) in two groups of early postmenopausal women. The boxes indicate the mean changes ±1 s.d. BMD_{QDR} and BMD_{DPA} denote the BMD of the lumbar spine measured by QDR (group B) and DPA (group A). BMC_{ARM} denotes the BMC of the forearm (group B).

obtained from QDR versus DPA indicates differences in the inaccuracy sources of the two systems. Kelly et al. and Wahner et al. recently published BMD values measured by DPA which were, respectively, ~20% and 10% higher than by QDR. Our DPA measurements differed only by 5%. The explanation is to be found in different software versions of the DPA. When we compared BMC values (i.e., the bone mass without interference from area determinations) obtained by DPA and QDR, the results were virtually similar.

The improved precision of the QDR compared to DPA only slightly improved the correlation between forearm BMC and spinal BMD. This suggests that the relatively weak correlation between appendicular and spinal BMD is mainly due to biologic variation and not to imprecision of the methods. Some of the variation may, of course, be caused by accuracy errors.

The ability of the methods to predict fracture risk was not investigated in the present study. But we did find that the ability to detect age-related bone loss was similar in the three methods. This implies, that the ability to predict fracture risk in later life is the same for all three methods.

Kelly et al. (*11*) and others (*12,13*) have demonstrated that the short-term in vivo precision of QDR was at least twice as good as that of DPA. The present study shows that this is also true for the long-term precision. The importance of a high reproducibility of a method in longitudinal trials was clearly demonstrated in the estrogen-progestogen trial. Here, the QDR technique was obviously superior to the DPA technique. The relevance of precision may be further illustrated by a simple theoretical calculation. If biologic variation is ignored, and a difference of 1% on a group basis is to be detected from two measurements on each subject, then a 1% precision demands 8 to 10 subjects, whereas a 3% precision demands 70 to 80 subjects (*18*). Although the biologic variation will increase these figures, and the former more than the latter, this example clearly demonstrates that high precision can save much in research.

We conclude that QDR provides a quick and precise measurement of spinal BMD. The in vivo accuracy of QDR has yet to be thoroughly investigated.

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