

Dual energy x-ray laser measurement of calcaneal bone mineral density

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Abstract

In dual energy x-ray absorptiometry (DXA) the photon attenuation is assumed to be similar in soft tissue overlying, adjacent to and inside the measured bone. In the calcaneal dual energy x-ray laser (DXL) technique, this assumption is not needed as attenuation by soft tissues at the local bone site is determined by combining DXA and heel thickness measurements. In the present study, 38 subjects were measured with DXL Calscan, Lunar PIXI and Lunar DPX-IQ DXA instruments and Hologic Sahara ultrasound instrument, and the performance and agreement of the instruments were analysed. Furthermore, numerical simulations on the effect of non-uniform fat-to-lean tissue ratio within soft tissue in heel were conducted. *In vivo* short-term precision (CV%, sCV%) of DXL Calscan (1.24%, 1.48%) was similar to that of Lunar PIXI (1.28%, 1.60%). Calcaneal areal bone mineral densities (BMD, g cm⁻²) measured using DXL Calscan and Lunar PIXI predicted equally well variations in BMD of femoral neck ($r^2 = 0.63$ and 0.52 , respectively) or lumbar spine ($r^2 = 0.61$ and 0.64 , respectively), determined with Lunar DPX-IQ. BMD values measured with DXL Calscan were, on average, 19% lower ($p < 0.01$) than those determined with Lunar PIXI. Interestingly, the difference in BMD values between instruments increased as a function of body mass index (BMI) ($r^2 = 0.17$, $p < 0.02$) or heel thickness ($r^2 = 0.37$, $p < 0.01$). Numerical simulations suggested that the spatial variation of soft tissue composition in heel can induce uncontrollable inaccuracy in BMD when measured with the DXA technique. Theoretically, in contrast to DXA instruments, elimination of the effect of non-uniform soft tissue is possible with DXL Calscan.

1. Introduction

Osteoporosis is most frequently diagnosed with dual energy x-ray absorptiometry (DXA). Unfortunately, measurement inaccuracy arising from the variable beam attenuation by non-uniform soft tissue composition may diminish the reliability of DXA measurements (Aloia *et al* 1995, Bolotin 1998a, Bolotin and Sievanen 2001, Bolotin *et al* 2001, Economos *et al* 1999, Lochmuller *et al* 2000, Patel *et al* 1997, Tothill *et al* 1997, Tothill and Pye 1992). In DXA, the effect of overlying soft tissue is taken into account by measuring attenuation with two x-ray energies in bone and soft tissue regions. By assuming a similar soft tissue contribution to attenuation in both regions, areal bone mineral density (BMD, g cm^{-2}) can be determined. The true soft tissue may consist, however, of both lean tissue and fat with non-uniform distribution. The difference between the attenuation coefficients of lean tissue and fat is significant, about 22% and 15% for the x-ray energies of 42 keV and 68 keV, respectively (Joyet *et al* 1974, Phelps *et al* 1975, Rao and Gregg 1975). Therefore, if the assumption on uniform soft tissue composition is incorrect, bone density will be over- or under-estimated in the DXA technique. Therefore over- or under-estimation of BMD is evident if the relative fat content in adjacent (baseline) soft tissue is different from that in soft tissue overlying bone. Furthermore, the composition of bone marrow can vary and affect the measured BMD value (Bolotin 1998b, Sorenson 1990). In commercial scanners a patient-specific soft tissue attenuation coefficient is derived and used when determining BMD (details on the correction procedures are usually proprietary information) (Sorenson 1990). However, small changes (<10%) in body weight may significantly affect ($\sim 2.5\%$) the measured bone mineral content (Patel *et al* 1997, Tothill *et al* 1997). Hangartner and Johnston (1990) suggested that patients with low bone density, e.g., elderly people, are subject to larger relative uncertainty in BMD measurements than patients with high bone density. Moreover, the small extraosseous fat-to-lean tissue ratio increases risk of underestimation of BMD (Bolotin and Sievanen 2001). Inaccuracy in BMD measurements due to variation in soft tissue composition has been demonstrated experimentally and by numerical simulations (Bolotin 1998a, Formica *et al* 1995, Hangartner and Johnston 1990, Sorenson 1990). In clinical measurements, errors in BMD, related to small non-uniform changes in soft tissue composition and thickness as well as to variable bone marrow composition, may exceed 20% (Bolotin and Sievanen 2001).

The inaccuracy in BMD, arising from the variable soft tissue composition, can be eliminated by determining the fat-to-lean tissue ratio at the measurement site. This can be done provided that the total tissue thickness at the measurement site is known (Jonson *et al* 1990). For calcaneal BMD, the DXL Calscan (Demetech AB, Solna, Sweden) accomplishes this by measuring the heel thickness with a laser reflection technique. A previous *in vitro* study (Kullenberg 2002) suggested that the dual x-ray laser (DXL) measurement enables more accurate measurement of BMD than the traditional DXA devices. In the present study we determined calcaneal BMD of the subjects using DXL Calscan and Lunar PIXI (Lunar Co, Madison, WI, USA) instruments. In addition, we evaluated the association between the calcaneal BMD, measured with these peripheral instruments, and the axial BMD, as determined for the same subjects with the Lunar DPX-IQ scanner (Lunar Co, Madison, WI, USA). For comparison, we carried out calcaneal ultrasound measurements using the Hologic Sahara instrument (Hologic Inc, Bedford, MA, USA). We were particularly interested to reveal whether the agreement between the devices is dependent on the potential variations in the soft tissue thickness and/or composition in heel, assumed to be reflected by a variable body mass index (BMI) of the subjects. In addition to experimental measurements, we simulated numerically calcaneal DXA measurement and focused on the errors in BMD values that could be related to variable soft tissue composition.

Table 1. Areal bone mineral density (BMD) in calcaneus, lumbar spine (L2–L4), femoral neck and total body as measured by different instruments (mean \pm SD). Results from the ultrasound measurements as well as age, body mass index (BMI) and heel thickness of the subjects are also shown.

Parameters	Mean \pm SD
Age (years)	59.7 \pm 9.4
BMI (kg m ⁻²)	26.5 \pm 3.7
DPX-IQ	
BMD (lumbar spine) (g cm ⁻²)	1.178 \pm 0.214
BMD (femoral neck) (g cm ⁻²)	0.940 \pm 0.170
BMD (total body) (g cm ⁻²)	1.195 \pm 0.118
DXL Calscan (calcaneus)	
BMD (g cm ⁻²)	0.452 \pm 0.095
Heel thickness (mm)	52.4 \pm 4.3
Lunar PIXI (calcaneus)	
BMD (g cm ⁻²)	0.565 \pm 0.114
Hologic Sahara (calcaneus)	
BUA (dB MHz ⁻¹)	81.5 \pm 22.9
SOS (m s ⁻¹)	1549.4 \pm 43.9
'Estimated BMD'	0.539 \pm 0.168

2. Materials and methods

2.1. Subjects and measurements

Calcaneal BMDs of the randomly selected subjects ($n = 38$, aged 59.7 ± 9.4 years, 18 males, 20 females) were measured with DXL Calscan (Demetech AB) and Lunar PIXI (Lunar Co) instruments. The physical basis of the DXL method is briefly presented in appendix A. BMDs in the proximal femur, lumbar spine (L2–L4) and total body were determined using a Lunar DPX-IQ scanner (Lunar Co.). Further, calcaneal speed of sound (SOS) and broadband ultrasound attenuation (BUA) were measured with Hologic Sahara (Hologic Inc). Based on the measured ultrasound parameters, 'estimated BMD' was determined by Hologic Sahara. In addition, 24, 11 and 10 subjects were measured with DXL Calscan, Hologic Sahara and Lunar PIXI, respectively, three times to determine the short-term precision of the instruments. All measurements were conducted along the instructions of the manufacturer. For each subject, body weight and height were measured and the body mass index (BMI) was determined. Heel thickness was obtained from the DXL measurement.

2.2. Numerical simulations

In vivo calcaneal DXA measurement was simulated numerically in order to estimate the inaccuracy related to determination of BMD (see appendix B). In simulations, a constant heel thickness ($d = 52.4$ mm, table 1) with a typical fat-to-lean tissue ratio (0.32, (Morabia *et al* 1999)) was used at the bone region. Calcaneus was assumed to be of constant thickness throughout the measurement area. Simulations were conducted with a wide range of BMD values (0.4–1.4 g cm⁻²) and normalized fat-to-lean tissue ratios (0.1–3, equation (B.10), appendix B). Values of mass attenuation coefficient ($\mu_{i,j}$) and density (ρ_i) were adopted

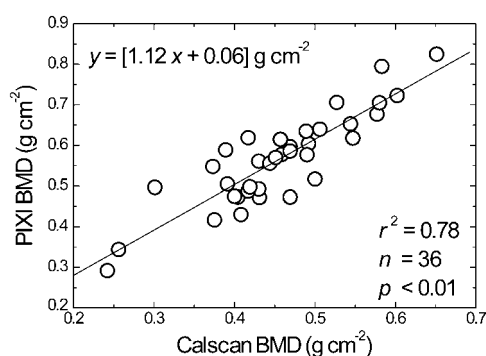


Figure 1. High linear correlation between the calcaneal BMD values determined with DXL Calscan and Lunar PIXI was revealed. However, the absolute BMD values measured with DXL Calscan were, on average, lower (−19%) than those measured with Lunar PIXI.

from the literature (Jonson 1993). Attenuation coefficients of glycerol trioleate (triolein), water and calcium hydroxyapatite were used to represent fat, lean tissue and bone tissue, respectively (Jonson 1993). X-ray energies ($E_1 = 40$ keV and $E_2 = 70$ keV) in the simulations correspond to typical energies used in clinical instruments, e.g., Lunar DPX scanner (Hangartner and Johnston 1990). The ratio of photon count rate transmitted through the bone (N_i) to the photon count rate without the bone ($N_{0,i}$) was calculated. The same procedure was repeated for the soft tissue (appendix B) in order to derive the soft tissue mass attenuation coefficient (equations (B.7) and (B.8)). Finally, BMD was calculated (equation (B.9)) by using the soft tissue mass attenuation coefficients and compared to the known BMD value (equation (B.11)).

2.3. Statistical analyses

The statistical difference between the BMD values determined with DXL Calscan and Lunar PIXI, was tested using the paired samples t-test. The short term precision of the instruments was determined in terms of a coefficient of variation (CV%) (Gluer *et al* 1995) and a standardized coefficient of variation (sCV%) (Njeh *et al* 2000). Linear correlation coefficients were determined using Pearson's correlation analysis. The statistical significance of differences between the correlation coefficients was tested using Student's t-test (Sokal 1981). Statistical analyses were conducted using SPSS 8.0 (SPSS Inc., Chicago, IL, USA) or Microsoft Excel (Microsoft Co., Redmond, WA, USA).

3. Results

The *in vivo* precision (CV%, sCV%) of DXL Calscan and Lunar PIXI were (1.24%, 1.48%) and (1.28%, 1.60%), respectively. For Hologic Sahara CV% and sCV% values were (4.09% and 3.64%) for BUA and (0.32% and 2.80%) for SOS.

A significant linear correlation between the calcaneal BMD values determined with DXL Calscan and Lunar PIXI was revealed ($r^2 = 0.78$, $n = 36$, $p < 0.01$, figure 1). BMD values measured with DXL Calscan were, however, on average 19% lower than those obtained with Lunar PIXI (0.452 ± 0.095 g cm^{−2} versus 0.565 ± 0.114 g cm^{−2}, mean \pm SD, $p < 0.01$, table 1,

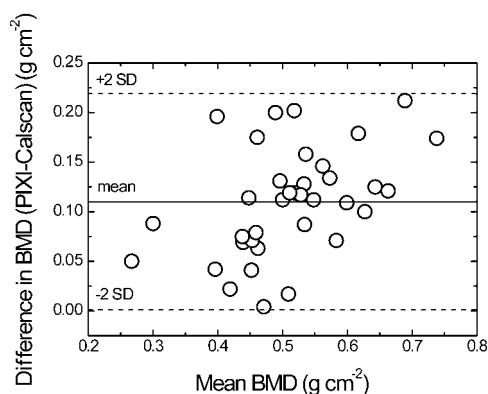


Figure 2. Bland–Altman plot for the calcaneal BMD values measured with DXL Calscan and Lunar PIXI. The difference of $0.110 \pm 0.109 \text{ g cm}^{-2}$ (mean $\pm 2 \text{ SD}$) is demonstrated in calcaneal BMD values.

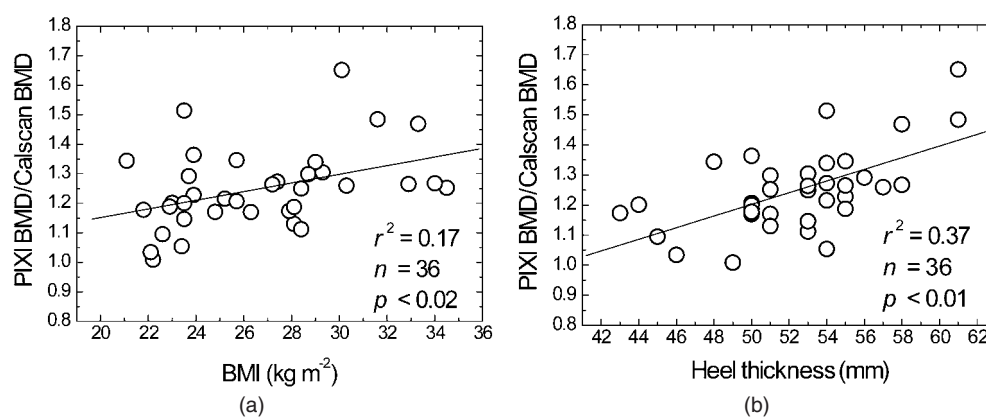


Figure 3. Ratio of calcaneal BMD values, determined with Lunar PIXI and DXL Calscan, as a function of body mass index and heel thickness. The BMD ratio increased as a function of BMI (kg m^{-2}) (a) or heel thickness (mm) (b).

figure 2). The difference in BMD values increased as a function of BMI ($r^2 = 0.17$, $n = 36$, $p < 0.02$, figure 3(a)) or heel thickness ($r^2 = 0.37$, $n = 36$, $p < 0.01$, figure 3(b)). Moderate linear correlations were revealed between the Hologic Sahara parameters and DXL Calscan BMD ($r^2 = 0.52$, $n = 34$, $p < 0.01$ for BUA, $r^2 = 0.53$, $n = 34$, $p < 0.01$ for SOS and $r^2 = 0.52$, $n = 36$, $p < 0.01$ for 'Estimated BMD', figure 4).

The calcaneal BMD, as measured with DXL Calscan or Lunar PIXI, correlated linearly with the BMD of femoral neck, lumbar spine or total body ($r^2 = 0.52$ – 0.76 , $p < 0.01$, $n = 36$ – 38 , table 2). The corresponding linear correlations between the axial BMD and BUA, SOS or 'Estimated BMD', as determined with Hologic Sahara, were not statistically different ($r^2 = 0.29$ – 0.45 , $p < 0.01$, $n = 34$ – 36 , table 2).

Numerical simulations of traditional DXA measurement revealed an increase in the relative BMD error as the normalized fat-to-lean tissue ratio increased, i.e. fat content was

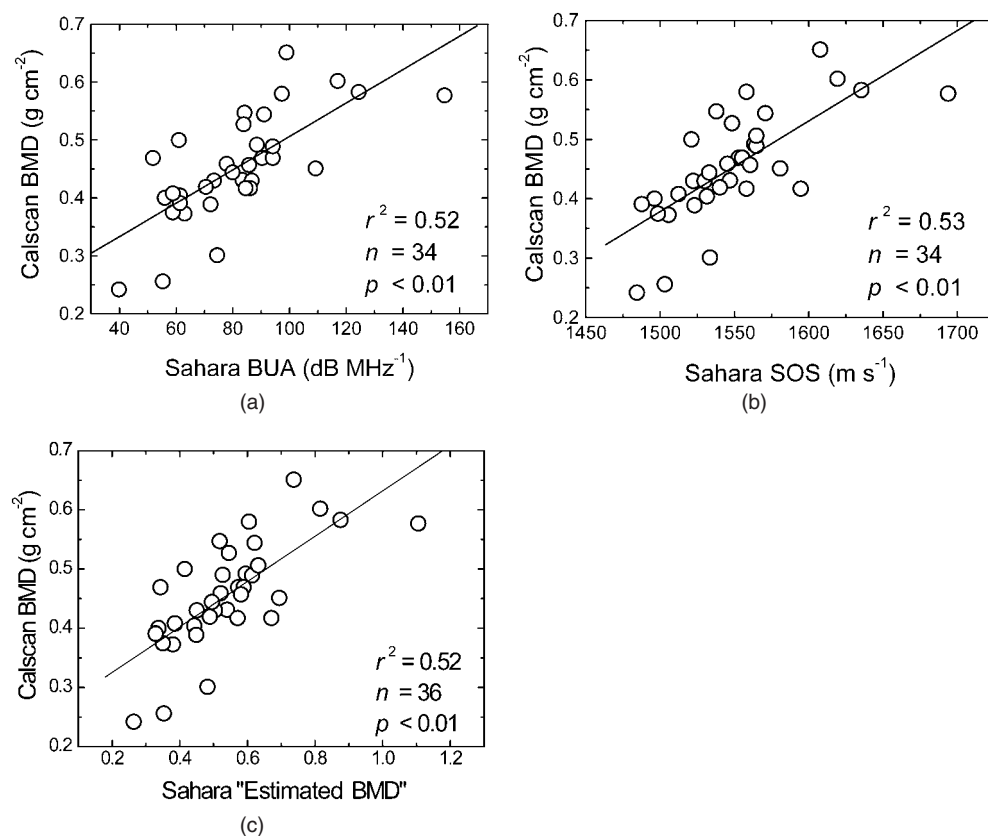


Figure 4. Linear correlations between calcaneal BMD (DXL Calscan) and (a) BUA (dB MHz⁻¹), (b) SOS (m s⁻¹) and (c) 'Estimated BMD' (Hologic Sahara).

Table 2. Linear correlation coefficients (r^2) between the lumbar spine, femoral neck and total body BMD (DPX-IQ) and calcaneal BMD (DXL Calscan and Lunar PIXI), heel thickness (DXL Calscan), calcaneal BUA, SOS and 'Estimated BMD' (Hologic Sahara).

	DPX-IQ		
	BMD (lumbar spine) (g cm ⁻²)	BMD (femoral neck) (g cm ⁻²)	BMD (total body) (g cm ⁻²)
DXL Calscan (calcaneus, $n = 38$)			
BMD (g cm ⁻²)	0.61*	0.63*	0.76*
Heel thickness (mm)	0.00	0.03	0.00
Lunar PIXI (calcaneus, $n = 36$)			
BMD (g cm ⁻²)	0.64*	0.52*	0.74*
Hologic Sahara (calcaneus, $n = 34-36$)			
BUA (dB MHz ⁻¹)	0.45*	0.35*	0.42*
SOS (m s ⁻¹)	0.41*	0.29*	0.42*
'Estimated BMD'	0.42*	0.32*	0.43*

* $p < 0.01$.

higher in the baseline than in the bone region (figure 5). Furthermore, the relative error in the measured BMD value increased as the true BMD value decreased (figure 5).

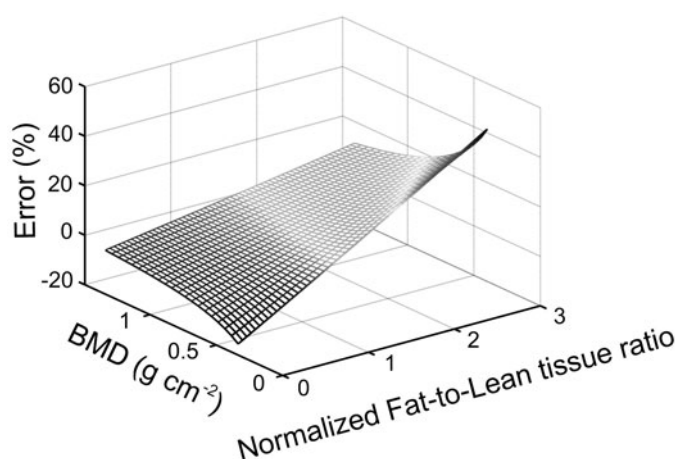


Figure 5. Relative error (%) in DXA-measured BMD value as a function of the true BMD (g cm^{-2}) value and normalized fat-to-lean tissue ratio ($= \text{Fat}_{\text{baseline}} (\%) / \text{Fat}_{\text{bone segment}} (\%)$). No error is found with normalized fat-to-lean tissue ratio value 1 (uniform soft tissue composition). The relative error increases as the true BMD decreases or the normalized fat-to-lean tissue ratio increases.

4. Discussion

In the present study a novel peripheral bone densitometer, DXL Calscan, was used for calcaneal BMD measurements of 38 subjects. For comparison, calcaneal, axial (lumbar spine and proximal femur) and total body BMDs were measured with Lunar DXA instruments. Further, calcaneal ultrasound measurements were conducted for the same subjects. The precision of the DXL Calscan was similar to that of Lunar PIXI. Calcaneal BMD values, as determined with DXL Calscan and Lunar PIXI, predicted similarly the variation of axial BMD measured with Lunar DPX-IQ. Despite the equally strong correlations with the axial BMD, differences in the calcaneal BMD values were detected (figure 2). BMD values measured with DXL Calscan were significantly lower, especially in subjects having high BMI, than the values measured by Lunar PIXI. This discrepancy in BMD values may be related to the differences in the measurement principles. This conclusion is supported by the numerical simulations revealing potential errors in DXA measured BMD values due to non-uniform soft tissue composition.

The technical performance of a clinical instrument is characterized by its precision and accuracy. In the present study, the precision of the DXL Calscan was similar to that of clinical calcaneal DXA devices (Fuleihan *et al* 1995, Johnson and Dawson-Hughes 1991, Sievanen *et al* 1992, Svendsen *et al* 1995). Earlier, Swanpalmer and Kullenberg (2000) demonstrated the accuracy of DXL Calscan to be similar (standard error of estimate ($\text{SEE}\%$) = 1.6%) or even better than that of axial DXA devices (typical $\text{SEE}\%$ for the distal femur 3%–6.7%) (Svendsen *et al* 1995). Moreover, *in vitro* measurement of bone phantoms showed an accuracy of 1.8–1.9% for DXL Calscan (Kullenberg 2002). In principle, the combination of two experimental measurements (DXA and laser) may reduce the overall precision due to the inherent uncertainty of each measurement. However, the present and earlier (Kullenberg 2002) studies reveal a good *in vivo* precision ($\text{CV}\% \leq 1.24\%$) of the DXL Calscan measurements.

A reliable diagnosis and sensitive monitoring of osteoporosis sets high demands on the performance of a clinical instrument. Due to the non-uniform changes in soft tissue composition, significant errors up to 0.1 g cm^{-2} (Tothill and Pye 1992) may be introduced in BMD when using the DXA technique. The error is approximately equal to ± 1 T-score

(one standard deviation above (+) or below (–) the average peak bone density in young adults), i.e. the same magnitude as the difference between the normal and osteopenic bone (Looker *et al* 1997) and can lead to diagnostic misinterpretation of the BMD measurement (Bolotin and Sievanen 2001). Especially, the measurement uncertainty induced by the changes in soft tissue composition, e.g., after significant weight gain or loss, jeopardizes the reliability of the longitudinal studies (Lochmuller *et al* 2000, Patel *et al* 1997, Phillipov *et al* 2001, Tothill *et al* 1997, Tothill and Pye 1992).

The difference between BMD values measured with DXL Calscan and Lunar PIXI was positively related to BMI and heel thickness, indicating that the elimination of soft tissue is different in the DXL and DXA instruments. In a two-component DXA method, complete elimination of the non-uniform soft tissue effect on BMD measurements is not possible (Sorenson 1990). The thickness of the human heel and composition of the overlying soft tissue vary significantly between individuals (Hausler *et al* 1997) and, possibly, also spatially within the heel. Our simulations revealed a similar trend for BMD inaccuracy as found earlier (Bolotin 1998a, Formica *et al* 1995, Hangartner and Johnston 1990). Non-uniform soft tissue thickness induces errors that can be captured from the present simulation by extrapolating the normalized fat-to-lean tissue ratio to values >3 (by increasing the heel thickness in baseline). In a three-component DXL technique the fat and lean tissue content in soft tissue overlying and inside the bone are determined (Jonson *et al* 1990). Compared to DXA, theoretically, measurement of the heel thickness minimizes error induced by the soft tissue on the measured calcaneal BMD.

'Estimated BMD' determined with Hologic Sahara accounted for 32–43% of the variation in the Lunar DPX-IQ measured axial BMDs, while the calcaneal BMD determined with DXL or DXA explained 52–76% of the variation. The 'Estimated BMD' is derived as a combination of BUA and SOS values, and does not indicate true areal mineral density (g cm^{-2}). However, the usefulness of the quantitative ultrasound technique has been demonstrated by its success in predicting osteoporotic fractures (Kroger *et al* 1995, Pfeifer *et al* 1997, Schott *et al* 1995). By definition the size of the measured bone affects DXA or DXL measured BMD values. Ultrasound parameters, SOS and BUA, are measured by using the substitution principle (Langton *et al* 1984) and demonstrate a linear positive relation to bone size. Since the interdependence between the bone size and DXA or ultrasound parameters is similar, linear correlations between the measured parameters may be apparently improved (Saarakkala *et al* 2002).

In conclusion, bone densitometry measurements are affected by overlying soft tissues and bone marrow. In DXA, the effect of variable soft tissue composition is reduced by making dual energy x-ray measurement at the soft tissue site adjacent to the actual region of interest. Since soft tissue thickness and composition may significantly vary between different regions of interest, it can induce uncertainty in the BMD results, as suggested by the present numerical simulations. The DXL technique enables determination of the fat-to-lean tissue ratio at the measurement site and minimizes, at least theoretically, the soft tissue induced distortion of measured BMD values. To conclude, our results suggest that the precision of DXL Calscan is similar to that of the current clinical instruments. In theory, DXL Calscan provides a more accurate measure of calcaneal BMD than traditional DXA instruments.

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Appendix A. DXL theory

In the dual x-ray laser (DXL) method the heel is scanned with x-ray energies of 35 keV and 70 keV. In addition, a laser reflection technique is used to determine heel thickness. The areal bone mineral density (BMD, g cm^{-2}), determined as a product of density and thickness, is calculated using the following equations (A.1)–(A.3):

$$N_1 = N_{01} e^{-\mu_{b,1} t_b - \mu_{l,1} t_l - \mu_{f,1} t_f} \rho_f \quad (\text{A.1})$$

$$N_2 = N_{02} e^{-\mu_{b,2} t_b - \mu_{l,2} t_l - \mu_{f,2} t_f} \rho_f \quad (\text{A.2})$$

$$T = t_b + t_l + t_f \quad (\text{A.3})$$

where N_1 and N_2 are the photon counts detected after x-rays pass through the measured object, N_{01} and N_{02} are the counts detected without the object, T is the total heel thickness and t_i indicates the thickness of each tissue component (b , l and f refer to bone⁶, lean tissue and fat, respectively). $\mu_{i,j}$ ($\text{cm}^2 \text{g}^{-1}$) is the mass attenuation coefficient (indices (b , $1/b$, 2), (l , $1/l$, 2) and (f , $1/f$, 2) refer to bone, lean tissue and fat at x-ray energies of 35 keV and 70 keV, respectively). ρ_i is the physical density (g cm^{-3}) of the corresponding (i) tissue. By measuring the heel thickness (T), bone thickness (t_b) can be determined from equations (A.1)–(A.3), provided that the densities of lean tissue and fat as well as the x-ray attenuation coefficients for each tissue component are known (Jonson *et al* 1990)

$$t_b = \frac{(R_1 \rho_f \mu_{f,2} - R_2 \rho_f \mu_{f,2}) \Delta_{l,f} - (R_2 - \rho_f \mu_{f,2} T) D_{l,f}}{D_{b,f} \Delta_{l,f} - D_{l,f} \Delta_{b,f}} \quad (\text{A.4})$$

where

$$R_1 = \ln \left(\frac{N_{01}}{N_1} \right) \quad R_2 = \ln \left(\frac{N_{02}}{N_2} \right)$$

$$D_{b,f} = \rho_b \mu_{b,1} \rho_f \mu_{f,2} - \rho_b \mu_{b,2} \rho_f \mu_{f,1}$$

$$D_{l,f} = \rho_l \mu_{l,1} \rho_f \mu_{f,2} - \rho_l \mu_{l,2} \rho_f \mu_{f,1}$$

$$\Delta_{b,f} = \rho_b \mu_{b,2} - \rho_f \mu_{f,2} \quad \Delta_{l,f} = \rho_l \mu_{l,2} - \rho_f \mu_{f,2}$$

Thus, by knowing the true density of calcium hydroxyapatite, areal bone mineral density (BMD, g cm^{-2}) can be derived

$$\text{BMD} = \rho_b t_b. \quad (\text{A.5})$$

Appendix B. Inaccuracies in calcaneal DXA measurement

In the DXA technique, equations (B.1) and (B.2) describe dual energy x-ray attenuation along a path passing through the bone,

$$N_1 = N_{0,1} e^{-M_b \mu_{b,1} - M_s \mu_{s,1}} \quad (\text{B.1})$$

$$N_2 = N_{0,2} e^{-M_b \mu_{b,2} - M_s \mu_{s,2}} \quad (\text{B.2})$$

⁶ In the DXL method the bone (b) component is the mineralized bone tissue, i.e. calcium hydroxyapatite.

where N_i and $N_{0,i}$ are the attenuated and unattenuated count rates with x-ray energy i (40 keV or 70 keV), respectively; M_i (g cm^{-2}) is the mass of a given constituent, $\mu_{i,1}$ and $\mu_{i,2}$ are the mass attenuation coefficients ($\text{cm}^2 \text{g}^{-1}$) for different constituents (subscript i) and x-ray energies. Indices b and s denote bone and soft tissue, respectively. While true soft tissue consists of at least two components, fat and lean tissue, the contents of soft tissue components can be estimated by measuring x-ray attenuation in soft tissue adjacent to the bone segment (baseline). X-ray attenuation in the soft tissue can be presented as follows:

$$I_1 = I_{0,1} e^{-M_l \mu_{l,1} - M_f \mu_{f,1}} \quad (\text{B.3})$$

$$I_2 = I_{0,2} e^{-M_l \mu_{l,2} - M_f \mu_{f,2}} \quad (\text{B.4})$$

where I_i and $I_{0,i}$ denote attenuated and unattenuated count rates. Subscripts f and l refer to fat and lean tissues, respectively. The masses (g cm^{-2}) of fat and lean tissue can be written

$$M_f = \frac{\left(\frac{\mu_{l,1}}{\mu_{l,2}}\right) \ln\left(\frac{I_2}{I_{0,2}}\right) - \ln\left(\frac{I_1}{I_{0,1}}\right)}{\mu_{f,1} - \mu_{f,2} \left(\frac{\mu_{l,1}}{\mu_{l,2}}\right)} \quad (\text{B.5})$$

$$M_l = \frac{\left(\frac{\mu_{f,1}}{\mu_{f,2}}\right) \ln\left(\frac{I_2}{I_{0,2}}\right) - \ln\left(\frac{I_1}{I_{0,1}}\right)}{\mu_{l,1} - \mu_{l,2} \left(\frac{\mu_{f,1}}{\mu_{f,2}}\right)}. \quad (\text{B.6})$$

Finally, effective mass attenuation coefficients for soft tissue can be estimated as a weighted average of fat and lean tissue mass attenuation coefficients

$$\mu_{s,1} = \frac{M_f \mu_{f,1} + M_l \mu_{l,1}}{M_f + M_l} \quad (\text{B.7})$$

$$\mu_{s,2} = \frac{M_f \mu_{f,2} + M_l \mu_{l,2}}{M_f + M_l}. \quad (\text{B.8})$$

Furthermore, the BMD can be determined

$$\text{BMD}(\text{g cm}^{-2}) = \frac{\left(\frac{\mu_{s,1}}{\mu_{s,2}}\right) \ln\left(\frac{N_2}{N_{0,2}}\right) - \ln\left(\frac{N_1}{N_{0,1}}\right)}{\mu_{b,1} - \mu_{b,2} \left(\frac{\mu_{s,1}}{\mu_{s,2}}\right)}. \quad (\text{B.9})$$

Non-uniformity of the soft tissue composition in bone segment and baseline can be modelled with a normalized fat-to-lean tissue ratio

$$\text{Normalized fat-to-lean tissue ratio} = \frac{\text{Fat}_{\text{baseline}} (\%)}{\text{Fat}_{\text{bone segment}} (\%)} \quad (\text{B.10})$$

where $\text{Fat}_{\text{baseline}}$ and $\text{Fat}_{\text{bone segment}}$ are the fat contents of soft tissue in baseline and bone segment, respectively. To illustrate potential inaccuracy in BMD due to the non-uniform soft tissue composition in bone segment and baseline, the relative error in BMD can be written

$$\text{Error} (\%) = \frac{\text{BMD}_{\text{estimated}} - \text{BMD}_{\text{true}}}{\text{BMD}_{\text{true}}} \times 100\% \quad (\text{B.11})$$

where $\text{BMD}_{\text{estimated}}$ and BMD_{true} refer to calculated and true BMD values, respectively.

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