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Evaluation of Osteoporosis Using Skin Thickness Measurements

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Abstract Measurement of skin thickness has been proposed as a method of predicting low bone mineral density (BMD) and the consequent risk of osteoporotic fracture in postmenopausal women. The Episcan I-100 device is a new type of ultrasound device that uses high-frequency (20 MHz) ultrasound to measure skin thickness using a small probe placed on the skin. The aims of this study were to investigate whether there is any correlation between skin thickness as measured by ultrasound and BMD as measured by dual-energy X-ray absorptiometry, to establish whether patients with osteoporotic fractures have reduced skin thickness, and to investigate the relationship between skin thickness and clinical risk factors for osteoporosis. Short-term precision based on duplicate measurements on 132 patients gave a coefficient of variation of 3.2%. Small but statistically significant correlations between skin thickness measurements and BMD measurements at axial and peripheral sites were observed (r = 0.21–0.29, $P <$ 0.0001). An odds ratio of 1.42 was found for identifying patients with a prevalent fracture at any skeletal site, suggesting that skin thickness measurements can discriminate patients with fractures. ROC analyses also demonstrated the ability of skin thickness measurements to discriminate fracture patients from controls. When measured by the decrease in Z-score, clinical risk factors for low BMD were found to affect skin thickness measurements to a similar extent as spine and hip BMD measurements. Skin thickness measurements have limited utility in identifying patients with low bone mass.

Keywords Bone mineral density · Fracture risk · Osteoporosis · Skin thickness

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Osteoporosis is a major public health concern in the United Kingdom and around the world because of the significant morbidity, mortality, and costs associated with its complications, namely fractures of the hip, spine, forearm, and other skeletal sites [1]. In recent years dual-energy X-ray absorptiometry (DXA) has become the most widely used technique for the assessment of osteoporosis based on measurements of bone mineral density (BMD) at the spine and hip. The reasons for this choice include the fact that hip BMD is the best predictor of hip fracture risk [2, 3], the use of spine BMD for monitoring treatment [4], and the widespread consensus that spine and hip BMD results should be interpreted using the World Health Organisation (WHO) definition of osteoporosis of a T-score of −2.5 or below [5, 6].

DXA scanners are relatively expensive pieces of equipment, and their availability is generally restricted to major hospitals [4]. If the diagnostic benefits of bone densitometry are to be fully realized, then smaller, cheaper, and ideally mobile devices are required. As well as DXA, a number of other techniques for the assessment of low bone mass have been proposed, ranging from risk factor questionnaires to quantitative ultrasound techniques for bone. Measurement of skin thickness has been proposed as a method of predicting low BMD and the consequent risk of osteoporotic fracture in postmenopausal women [7]. The

organic matrix of mineralized bone is comprised of 90% collagen, primarily of type I [8]. In skin also, type I collagen represents the major fibrous structure of the dermis [9]. Similar factors may determine both dermal thickness and bone mass because of this common organic constituent. Age-related loss of bone mass and skin atrophy are well documented, and the impact of menopause on both has been extensively reported. Several authors have postulated that the connective tissue might be a common factor behind the postmenopausal changes in bone and skin. Albright et al. [10] first reported that elderly women with osteoporotic fractures had a higher incidence of thin skin. In 1963 McConkey et al. [11] reported that osteoporosis was more common in women with transparent (thin) skin than in women with opaque skin. They also suggested that both osteoporosis and transparent skin were the result of the same connective tissue disorder. Subsequently, Orme and Belchez [7] demonstrated a lower mean skinfold thickness (measured using calipers) in osteoporotic compared to normal women.

High-frequency (20 MHz) ultrasound has been shown to be an accurate method for measuring skin thickness [12, 13]. The aims of this study were to evaluate the reproducibility of skin thickness measurements using a high-frequency ultrasound probe, to investigate whether there is any correlation between skin thickness as measured by ultrasound and BMD as measured by DXA, to establish whether patients with prevalent osteoporotic fractures have reduced skin thickness, and to investigate the relationship between skin thickness and clinical risk factors for osteoporosis.

Subjects and Methods

The Episcan I-100 device (Fig. 1) is a novel type of ultrasound device that uses high-frequency (20 MHz) ultrasound to measure skin thickness. It is a compact unit using a small probe placed on the skin with ultrasound gel. Measurements at the mid-forearm (anterior site) (Fig. 1) were performed in 603 white U.K. women. Exposure to sunlight is known to have an adverse affect on skin thickness, and the anterior site was chosen as it is less exposed to sunlight than the posterior part of the forearm. The mid-anterior site was chosen as measurements at this site were found to be more reproducible compared to measurements at the distal or proximal sites. The Episcan system displays the information obtained in the form of brightness or B-scans [14], which are presented as high-quality color-coded images (Fig. 2).

Out of the 603 women participating in the study, 98 had previously sustained a low trauma fracture. A further 356 were women with risk factors (other than fracture) who had been referred by their general practitioner (GP) or hospital consultant for a routine DXA bone density scan. The remaining 149 subjects formed a control group of normal healthy women from the general population without risk factors for osteoporosis who had volunteered to participate in clinical research. All the women completed a self-administered questionnaire. Women across a wide age range (20–81 years) were included, and 169 were pre-menopausal. The study was approved by the local research ethics committee.

DXA scans of the lumbar spine (L1–L4) and left proximal femur were performed using a Hologic QDR-4500 system (Hologic, Bedford, MA). BMD measurements of the distal forearm (radius plus ulna) were performed using an Osteometer DTX-200 peripheral DXA (pDXA) system

Fig. 1 Episcan I-100 measurement site

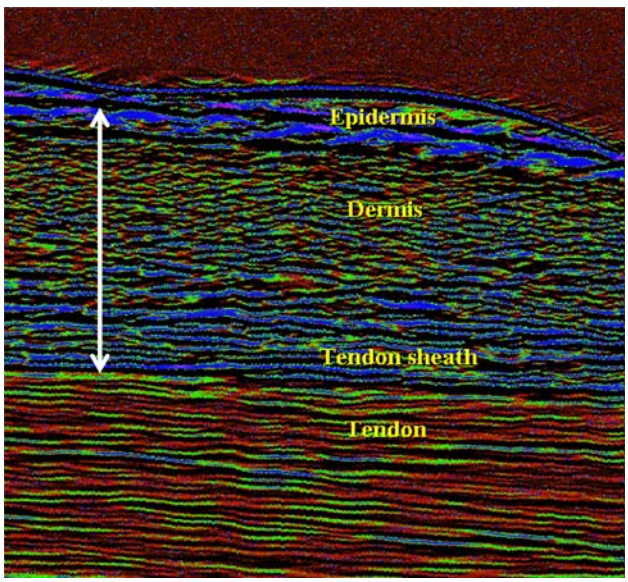

Fig. 2 Ultrasound image of skin thickness obtained using the Episcan I-100

(Osteometer Meditech, Hawthorne, CA). All BMD scan analyses were performed according to the manufacturers' standard protocols. The manufacturers' reference ranges for the spine and forearm sites were used to convert the BMD results into T-score values. The National Health and Nutrition Examination Survey (NHANES) reference range was used to calculate T-scores for the hip [15].

One hundred and thirty-two patients had duplicate measurements of skin thickness, with repositioning of the ultrasound probe between measurements. In vivo intraobserver short-term precision of Episcan I-100 skin thickness measurements was calculated as the coefficient of variation: %CV = (standard deviation/mean) × 100. Results for individual patients were combined as the root mean square (RMS) CV.

A series of studies were undertaken to evaluate the clinical value of Episcan skin thickness measurements in the investigation of osteoporosis.

Correlation with Spine and Hip BMD

Linear regression analysis was used to determine the relationship between skin thickness measurements and BMD at different sites. Since it is possible that the correlation between skin thickness and BMD measurements may be affected by the inclusion of patients with fractures, regression analysis was repeated after excluding women with a history of previous fracture.

Fracture Prediction

Of the 603 women in the study population, 98 postmenopausal women reported a previous low trauma fracture. A total of 111 fractures were reported including 50 Colles fractures and 15 vertebral fractures. Fracture patients included patients from the Guy's Hospital Metabolic Bone Clinic and referrals from GPs. All patients completed a questionnaire from which information relating to previous fractures was obtained. One hundred and forty-nine postmenopausal women without fractures or other risk factors for osteoporosis were used as the control group. Fracture discrimination was determined using age-adjusted logistic regression. This model was used to calculate the odds ratio per standard deviation (SD) decrease in measurement variable and the 95% confidence interval (CI). Logistic regression was also repeated after adjusting for BMI as well as age. The utility of skin thickness measurements was also examined by receiver operating characteristic (ROC) analyses. The area under the curve (AUC) was calculated for skin thickness measurements when osteoporosis was defined using the lowest T-score from the spine, femoral neck, and total hip sites. The fracture discrimination capability of each measurement site was also examined using ROC curves by comparing the respective AUC to directly comparing diagnostic performance.

Risk Factor Analysis

The aim of this part of the study was to compare skin thickness measurements with BMD measurements in a large group of women, some with no clinical risk factors and others with one or more risk factors for low BMD. Women in the study were placed into the following eight groups according to which clinical risk factor they had: (1) atraumatic fracture since the age of 25 years, (2) report of X-ray osteopenia, (3) predisposing medical condition or use of therapy known to affect bone metabolism, (4) premature menopause before the age of 45 years or a history of amenorrhea of longer than 6 months' duration, (5) maternal history of hip fracture, (6) body mass index (BMI) <20 kg/m^2, (7) use of oral corticosteroids, and (8) current smoking habit. The first six risk factors are listed in the Royal College of Physicians guidelines for the prevention and treatment of osteoporosis [16]. For the present study, a maternal history of fracture at the spine, hip, or forearm was used rather than hip fracture alone. Current smoking habit was also included as it is listed in the European Foundation of Osteoporosis and Bone Disease guidelines [17] and the National Osteoporosis Foundation guidelines [18] for identifying individuals at risk of fracture. Women who were currently prescribed (or had previously taken) treatment for osteoporosis were not excluded from the analysis. Women taking oral corticosteroid therapy (for greater than 6 months) were not included as part of the group consisting of women with a predisposing medical condition or therapy known to affect bone metabolism. As corticosteroid therapy is known to have an adverse affect on skin thickness, these women were treated as a separate group. Women on hormone replacement therapy (HRT) were also identified as a separate group as estrogen therapy is known to increase skin thickness.

Of the 603 women, 232 had none of the risk factors described above. Manufacturers' reference ranges were used to calculate Z-scores for the spine and the forearm. The NHANES reference range was used to calculate Z-scores for the hip. Z-scores for skin thickness measurements were calculated using the mean and SD for the nonfracture (pre- and postmenopausal) patients.

In order to confirm that the skin thickness data were normally distributed, statistical tests for skewness and kurtosis were performed. Student's *t*-test was used to

compare the pre- and postmenopausal groups with and without risk factors. $P < 0.05$ were considered to be statistically significant. The relationship between Z-score values and clinical risk factors was investigated using multivariate regression analysis to calculate the regression coefficient associated with each of the eight clinical risk factors using the following equation:

$$Z - score = b_0 + \sum_i b_i RF_i \quad (1)$$

In equation 1 each risk factor is represented by an independent variable, RF_i, that is set to 1.0 if the risk factor is present in a subject and 0 otherwise. When the equation is solved for all 603 women, the constant term b_0 represents the mean Z-score for the women with no clinical risk factors, while the regression coefficient b_i represents the mean decrease in Z-score associated with the ith risk factor.

Results

Characteristics for all 603 women are shown in Table 1. Duplicate measurements on 132 patients were combined to give an intraobserver short-term precision of 3.2% for ultrasound measurements of skin thickness using the Episcan I-100.

Linear regression analysis was used to examine the relationship between BMD and skin thickness measurements on the Episcan I-100 for all 603 subjects (Fig. 3). Small but statistically significant correlations were observed between skin thickness and BMD measurements (spine $r = 0.22$, standard error of estimate [SEE] = 0.16 g/cm^2; femoral neck $r = 0.23$, SEE = 0.14 g/cm^2; total hip $r = 0.29$, SEE = 0.15 g/cm^2; forearm $r = 0.21$, SEE = 0.08 g/cm^2; for all sites $P < 0.0001$). The correlation coefficients did not change when the regression analysis was repeated for nonfracture patients alone.

The variation in skin thickness with age is shown in Figure 4 for women up to the age of 80 years. The slope of −0.00014 mm/year (95% CI −0.00089 to 0.00061) was not significant ($P = 0.71$), and the correlation coefficient was very low ($r = 0.015$). The mean value of skin thickness remained constant from age 20 to 80 years. This remained true when patients taking HRT were excluded. For calculating Z-scores from skin thickness values, the mean and SD of 232 postmenopausal women without any clinical risk factors for osteoporosis were used. The mean skin thickness for this control group was 0.907 mm, with an SD of 0.130 mm.

The results of logistic regression analysis are given in Table 2, which shows the age-adjusted odds ratios for BMD and skin thickness measurements associated with

Table 1 Study group characteristics (mean and SD)

Age group (years)	n	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Lumbar spine BMD (g/cm^2)	Femoral neck BMD (g/cm^2)	Total hip BMD (g/cm^2)	Forearm BMD (g/cm^2)	Skin thickness (mm)
20–29	55	25.6 (2.8)	164.9 (6.4)	61.8 (9.9)	24.9 (1.3)	1.003 (0.133)	0.829 (0.104)	0.930 (0.117)	0.421 (0.047)	0.859 (0.115)
30–39	51	34.6 (3.0)	164.6 (6.5)	65.2 (16.3)	24.1 (6.1)	0.986 (0.134)	0.785 (0.149)	0.888 (0.154)	0.429 (0.068)	0.824 (0.131)
40–49	89	45.1 (2.7)	162.4 (6.5)	66.9 (14.1)	25.4 (5.1)	0.991 (0.133)	0.781 (0.115)	0.900 (0.132)	0.437 (0.059)	0.881 (0.141)
50–59	138	54.7 (2.8)	163.2 (6.5)	67.5 (12.4)	25.4 (4.6)	0.965 (0.162)	0.756 (0.133)	0.892 (0.136)	0.430 (0.082)	0.906 (0.137)
60–69	164	64.9 (3.0)	160.1 (6.6)	66.1 (12.5)	25.8 (5.0)	0.874 (0.172)	0.686 (0.126)	0.807 (0.147)	0.370 (0.074)	0.870 (0.155)
70+	106	74.1 (3.1)	157.5 (6.0)	61.2 (11.84)	24.6 (4.5)	0.843 (0.162)	0.626 (0.114)	0.736 (0.130)	0.326 (0.068)	0.840 (0.128)

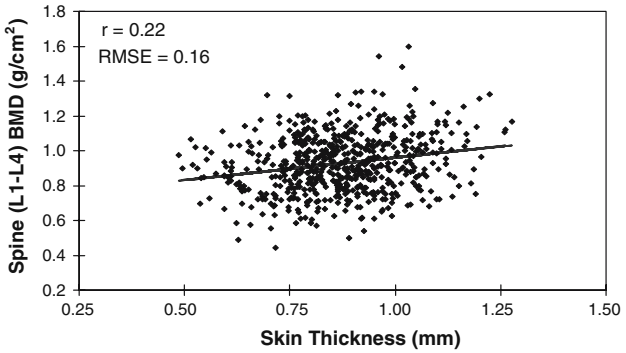

Fig. 3 Correlation of skin thickness with lumbar spine (L1–L4) BMD

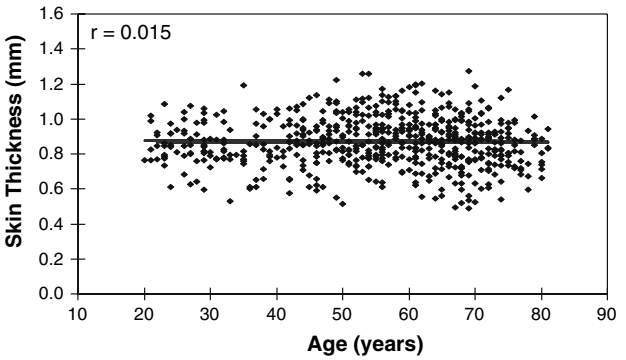

Fig. 4 Variation of skin thickness with age (n = 603)

any type of low trauma fracture, vertebral fracture, and Colles fracture. Skin thickness measurements yielded a statistically significant result for identifying women with any type of fracture with a relative risk (odds ratio/SD) value of 1.42 ($P < 0.001$, 95% CI 1.13–1.77). When logistic analysis was repeated with adjustment for age and BMI, the results did not change. The ROC curve for skin thickness measurements when osteoporosis was defined using the lowest T-score from the spine, femoral neck, and total hip sites gave an AUC value of 0.593. When osteoporosis was defined as the lowest T-score from just the spine and total hip sites, the AUC was 0.579. The AUC values from the ROC curves for fracture prediction are shown in Table 3.

Table 3 Areas under ROC curves

	All fractures	Vertebral fractures	Colles fractures
Lumbar spine BMD	0.63	0.76	0.54
Femoral neck BMD	0.70	0.74	0.69
Total hip BMD	0.71	0.81	0.68
Forearm BMD	0.60	0.67	0.57
Skin thickness	0.64	0.66	0.62

Statistical tests on the skin thickness measurements for skewness and kurtosis were not significant, confirming that the data followed a gaussian distribution pattern. Characteristics for pre- and postmenopausal women are shown in Table 4 for women with and without clinical risk factors. Both pre- and postmenopausal women with clinical risk factors for osteoporosis had significantly lower skin thickness compared to women without risk factors. Women with a history of atraumatic fracture and women with X-ray osteopenia were older than women with other risk factors. Women with a BMI <20 kg/m^2 and women who smoked were younger compared to women with other clinical risk factors. Results of multivariate regression analysis were used to examine the mean decrease in Z-score associated with each clinical risk factor for the whole population (Fig. 5). The Z-score decreases associated with the various risk factors were similar for forearm and axial (spine and hip) BMD measurements. For skin thickness measurements, Z-score decreases associated with a history of atraumatic fracture (−0.35), a medical condition or therapy (excluding corticosteroid use) known to affect bone metabolism (−0.43), corticosteroid use (−1.01), premature menopause or history of amenorrhea (−0.21), and a BMI <20 kg/m^2 (−0.34) were all statistically significant compared to women with no risk factors. Women on HRT showed a significant increase in Z-score (+0.22).

Table 2 Age-adjusted odds ratios for BMD and skin thickness measurements associated with any low trauma fracture, vertebral fracture, and Colles fracture

	Odds ratio (95% CI) (all low trauma fractures, n = 98)	Odds ratio (95% CI) (vertebral fractures, n = 15)	Odds ratio (95% CI) (Colles fractures, n = 50)
Lumbar spine BMD (g/cm^2)	1.6 (1.2–2.0)	3.0 (1.5–6.1)	1.2 (0.9–1.7)*
Femoral neck BMD (g/cm^2)	2.0 (1.5–2.7)	3.2 (1.4–7.3)	2.3 (1.5–3.6)
Total hip BMD (g/cm^2)	2.1 (1.6–2.7)	4.0 (1.9–8.4)	2.1 (1.4–3.0)
Forearm BMD (g/cm^2)	2.1 (1.5–2.8)	2.9 (1.4–6.1)	1.8 (1.2–2.7)
Skin thickness (mm)	1.4 (1.1–1.8)	1.9 (1.1–3.2)	1.4 (1.0–1.9)

*P not significant. $P < 0.05$ for all other measurements

Table 4 Patient characteristics for risk factor analysis

	Premenopausal without risk factors	Premenopausal with risk factors	Postmenopausal without risk factors	Postmenopausal with risk factors
n	83	86	149	285
Age (years)	36.3 (9.9)	36.4 (8.8)	62.7 (8.1)	62.9 (9.7)
BMI (kg/m^2)	25.6 (4.7)	23.1 (5.4)	25.6 (3.9)	25.0 (5.1)
Spine (L1–L4) BMD (g/cm^2)	1.056 (0.099)	0.961 (0.133)*	0.898 (0.163)	0.895 (0.176)
Femoral neck BMD (g/cm^2)	0.856 (0.098)	0.767 (0.120)*	0.709 (0.122)	0.686 (0.140)†
Total hip BMD (g/cm^2)	0.973 (0.095)	0.869 (0.136)*	0.844 (0.140)	0.802 (0.154)†
Forearm BMD (g/cm^2)	0.451 (0.054)	0.416 (0.059)*	0.389 (0.081)	0.376 (0.086)†
Skin thickness (mm)	0.914 (0.118)	0.823 (0.141)*	0.903 (0.137)	0.855 (0.142)†
%Treated	3	14	34	23

*$P < 0.05$ vs. premenopausal women without risk factors. $^\dagger P < 0.05$ vs. postmenopausal women without risk factors

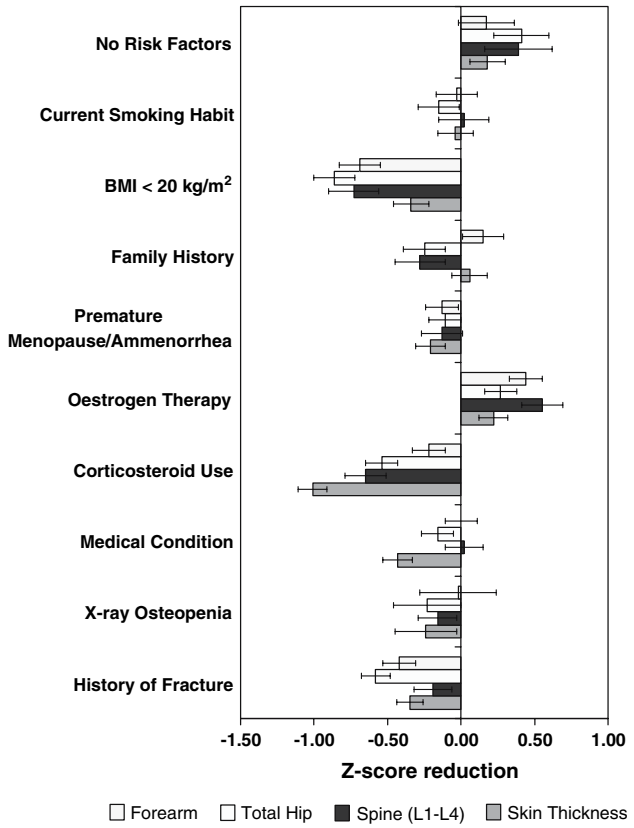

Fig. 5 Z-score coefficient associated with each clinical risk factor for the whole study population

Discussion

In the present study, weak but statistically significant correlations were observed between skin thickness and BMD. The correlation coefficient varied from $r = 0.21$ for the forearm site to $r = 0.29$ for the total hip site. These figures were unchanged when the coefficients were calculated for nonfracture patients only. Few other studies have examined the correlation between skin thickness and bone mass. Brincat et al. [19] reported a significant correlation ($r = 0.4$) between skin thickness measured on radiographs of the forearm and metacarpal index. Chappard and colleagues [20] reported similar correlations between skin thickness measured with calipers on the dorsum of the hand and spine and hip BMD measured using DXA. Varila et al. [8] used high-frequency (20 MHz) ultrasound measurements of skin thickness to investigate whether such measurements could predict low BMD and the risk of osteoporosis in peri- and postmenopausal women. Although significant correlations ($r = 0.43$–0.50) were observed, the authors concluded that there was only a loose association between skin thickness and BMD at any site. Smeets et al. [21] investigated whether skin thickness measurements by ultrasound could be used for screening for low bone mass in postmenopausal women. The correlations between skin thickness at the forearm and BMD at the lumbar spine (measured by quantitative computed tomography) and hand (measured using quantitative video microdensitometry) were found to be weak, and the results were not statistically significant. This led the authors to conclude that skin thickness does not reflect BMD in postmenopausal women. The correlation coefficients observed in the present study, although statistically significant, leave >90% of the variability between skin thickness and BMD measurements unexplained, suggesting that a skin thickness measurement is only a weak predictor of bone density.

A weak correlation between skin thickness and BMD does not necessarily mean that skin thickness cannot independently predict fracture risk, and one of the aims of the present study was to establish if skin thickness measurements discriminate patients with a history of previous fracture. Odds ratios reported as the increase in risk per SD decrease in skin thickness were compared to odds ratios obtained from spine, hip, and pDXA measurements. Skin thickness measurements yielded statistically significant odds ratios for identifying women with spine, forearm, or any type of fracture. This is the first study to demonstrate the ability of skin thickness measurements to discriminate fracture patients from

controls. However, the magnitude of the odds ratios for skin thickness measurements was considerably smaller than the odds ratios obtained for axial BMD sites and for forearm BMD, suggesting only weak fracture discrimination. In order to establish whether skin thickness measurements provide additional information for fracture discrimination after adjustment for clinical risk factors, logistic regression analysis was repeated with adjustment for BMI and age. Odds ratios for skin thickness measurements remained unchanged when the adjustment for age and BMI was included. This suggests that when estimating fracture risk skin thickness may provide independent information to that obtained from clinical risk factors. The ability to identify fracture cases was also examined using ROC analyses. The AUC confirmed the limited utility of skin thickness measurements for identifying patients with osteoporosis and identifying fracture cases.

Many of the clinical risk factors for osteoporosis, such as history of maternal hip fracture and estrogen deficiency, are associated with reduced BMD. There is clear evidence that DXA measurements of BMD in the axial skeleton are significantly lower in individuals with clinical risk factors for osteoporosis [22, 23]. One aim of the present study was to determine whether skin thickness measurements are affected by clinical risk factors in a similar manner to BMD measurements. Results of multivariate regression analysis showed that for skin thickness measurements the Z-score associated with a history of atraumatic fracture, a medical condition or therapy known to affect bone metabolism, corticosteroid use, premature menopause or history of amenorrhea, and BMI <20 kg/m^2 were all significantly reduced compared to women with no risk factors. Women with a history of atraumatic fracture and a BMI <20 kg/m^2 also had significantly reduced BMD in the forearm and at axial sites. Women on corticosteroid therapy had reduced BMD at the spine and hip but not at the forearm. However, all other risk factors did not result in significantly lower BMD at peripheral or axial sites. Figure 5 demonstrates that skin thickness measurements vary in a similar manner to Z-scores at axial sites.

There is strong evidence that skin thickness is affected by corticosteroid use [24–26]. It was therefore decided to include women who had taken oral corticosteroids for 6 months or longer as a separate group from women identified as having other medical conditions or therapies known to affect bone metabolism. Approximately 12% of the women who were initially identified as having a medical condition or therapy known to affect BMD were on corticosteroid therapy. Results from the present study confirmed a reduction in skin thickness of approximately 1 SD associated with corticosteroid use. There was also a statistically significant reduction in BMD in these women at all axial sites but not at the forearm.

It is known that a decline in estrogen levels leads to thinning of the skin [27, 28], and a number of studies have demonstrated higher skin thickness in women on estrogen therapy [29–32]. This is the most likely reason for skin thickness being significantly reduced in women with a history of amenorrhea or premature menopause. When women on HRT were included as a separate group in the multivariate regression model, a statistically significant increase in skin thickness was observed. An increase was also observed in BMD at axial and peripheral sites.

Conclusions

In summary, statistically significant but weak correlations between skin thickness measurements and DXA measurements at axial and peripheral sites were observed. These low correlations suggest that skin thickness measurements are too poor predictors of BMD to have a role in identifying patients with low bone mass. Skin thickness measurements demonstrated significant but modest fracture discrimination, with a relative risk value (odds ratio/SD) of 1.42 for identifying women with any type of fracture. Clinical risk factors for osteoporosis were found to reduce skin thickness measurements to a similar extent as axial BMD when assessed in terms of the effect on Z-scores. The present study provides encouraging initial data but needs to be extended to better determine the relationship between skin thickness and BMD. Prospective studies are required to help determine more precisely the ability of skin thickness measurements to predict fracture risk in a larger population.

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