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Original Article

Longitudinal Changes in Ultrasound Parameters of the Calcaneus

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Abstract. We examined with a median follow-up of 1.4 years (range 1.0–2.0 years) the rates of change per year in ultrasound parameters of the calcaneus. Speed of sound (SOS), Broadband ultrasound attenuation (BUA) and Stiffness were measured twice in 543 subjects (224 men) participating in the Rotterdam Study. SOS fell by −2.5 m/s per year in both sexes (95% CI −4.0 to −1.1 m/s per year in men and −3.6 to −1.4 m/s per year in women). Stiffness decreased by −0.62 (−1.33 to 0.09) per year in men and −0.66 (−1.24 to −0.08) per year in women. In men the rate of change in SOS and Stiffness tended to increase with age. BUA did not change significantly during follow-up in either sex. The prospectively assessed rates of loss differed considerably from those observed cross-sectionally, especially for SOS in men (cross-sectional −0.7 m/s per year, longitudinal −2.5 m/s per year). There was substantial variation between individuals both in changes per year in SOS and in changes per year in BUA. With a median follow-up time of 1.4 years, approximately 27% of the variation in the rate of change for SOS could be explained by measurement error while for BUA this was approximately 9% and for Stiffness 11%. Only a small percentage of subjects had changes larger than could be accounted for by measurement error (SOS: men 26.8%, women 21.6%; BUA: men 28.5%, women: 38.8%; Stiffness: men 32.6%, women 35.1%). The latter may limit the use of ultrasound measurements as a follow-up tool in individuals rather than in populations.

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Introduction

Osteoporosis is characterized by loss of bone quantity and bone quality, leading to fractures by low-energy trauma [1]. It has been suggested that ultrasound parameters provide information on both qualitative and quantitative aspects of bone tissue [2]. This potential advantage, together with the fact that ultrasound measurements are radiation-free and relatively inexpensive, would make them valuable tools in assessing the risk of osteoporotic fractures.

Previous cross-sectional studies have indicated a substantial apparent decline in ultrasound parameters with age [3–6], which is in accordance with the age-related decline in bone mass as observed by bone mineral mass measurements [7]. Cross-sectional studies, however, may give a biased estimate of the true rate of loss [8]. Conflicting results from such studies may reflect cohort effects or survivor bias. Some of these biases may adequately be controlled for in longitudinal studies.

In the current study we examined changes in the ultrasound parameters speed of sound (SOS), broadband ultrasound attenuation (BUA) and Stiffness determined by longitudinal measurements in a group of men and women aged 55 years or over and compared them with the cross-sectional estimated rate of change, as well as with the rates of change in bone mineral density measured at the proximal femur.

Materials and Methods

Population

The Rotterdam Study is a prospective cohort study of people aged 55 years or over; its intent is to investigate the incidence of and the risk factors for chronic disabling diseases. Its rationale and design have been described previously [9]. All 10275 inhabitants, aged 55 years or over of a district in Rotterdam, The Netherlands, were invited to participate in this study. The study at baseline consisted of an initial home interview by a trained research assistant and a series of medical examinations during two visits to the research centre. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent has been obtained from all participants. The overall response rate for the Rotterdam Study was 78%.

Measurements

Since September 1992, ultrasound measurements have formed part of the Rotterdam Study protocol. Follow-up ultrasound measurements were performed between March and December 1994. In the present study, longitudinal changes in ultrasound measurements of all 543 subjects (224 men, 319 women) on which we had follow-up ultrasound data will be described.

SOS, BUA and Stiffness at the right heel were measured using a Lunar Achilles Ultrasound bone densitometer. The system consists of a water tank containing two broadband ultrasonic transducers. The heel is placed in the water bath and, after scanning, the SOS and net attenuation are calculated by a computer program, correcting for the influence of water. Stiffness is not a true measurement, but rather a mathematical combination of SOS and BUA. The coefficient of variation, calculated from 13 cohort members scanned twice on the same day, was 0.5% for SOS, 2.3% for BUA and 3.0% for Stiffness. The standardized coefficient of variation, defined as the coefficient of variation divided by the ratio of the range (5–95%) over the mean of the measurement [10] was 6.0% for SOS, 6.1% for BUA and 4.5% for Stiffness.

Calibration was performed daily. During follow-up there was an upward trend in the calibration values for SOS and a downward trend in the calibration values for BUA which, according to the manufacturer, was due to a slight narrowing of the distance between the transducers (Fig. 1). However, after calibration no drift was detected in the ultrasound parameters of a phantom which was regularly scanned at room temperature. This indicates that the daily calibration corrected for this narrowing is the distance between the transducers.

Bone mineral density was measured at the femoral neck, Ward's triangle and greater trochanter using a Lunar DPX-L densitometer as described previously [3].

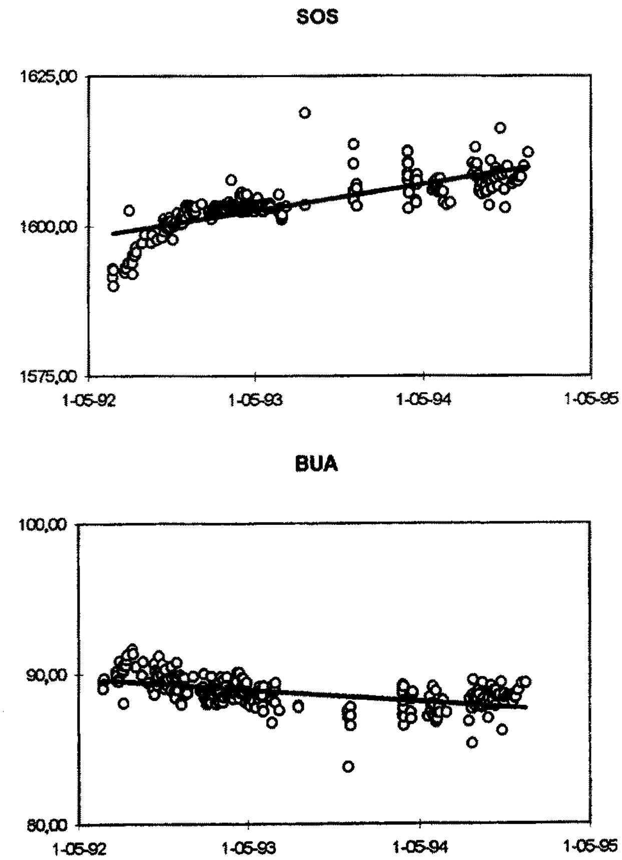

Fig. 1. Calibration drift in time for SOS and BUA respectively.

Data Analysis

An annual change in SOS, BUA and Stiffness was calculated by in each case subtracting the second measurement from the first and dividing the result by the follow-up time in years. A percentage annual change was calculated by dividing the above results by the average of the first and the second measurement (for SOS after subtraction of 1400 m/s initial value) [3]. Linear regression analysis was performed to estimate an effect of age, years since menopause, body mass index and baseline disability on longitudinal rates of change. Pearson's product moment correlation coefficients were calculated between the rates of loss for ultrasound parameters and bone mineral density measured at the proximal femur. We calculated the percentage of subjects that had an absolute difference between the first and the second measurement larger than 2 standard deviations of the difference of two measurements performed on the same day (for SOS >15.3 m/s, for Stiffness >4.8, and for BUA >5.06 dB/MHz). This was done to estimate the percentage of subjects with an absolute rate of change above that which could easily be accounted for by measurement error. Using a similar approach, the follow-up time necessary to state that the direction of a change per year in an individual can not be accounted for by measurement error was calculated. In other words, how long will it take, for various rates of change, to achieve a difference between two measurements of at least 15.3 m/s for SOS, 4.8 for Stiffness and 5.06 dB/MHz for BUA? For reasons of simplicity we did not take into account in the analysis that the rates of change may vary with time and that the degree of measurement error may depend on the level of the parameter studied.

Total variability in the rates of change is the sum of true variability and variability due to measurement error ($Var_{tot} = Var_{true} + Var_{error}$). By dividing the measurement error variability by the total variability we estimated the percentage of the variability that could be explained by measurement error (% due to error = $Var_{error}/Var_{tot} \times 100$).

Data are presented with the 95% confidence interval in parentheses. Negative values for mean change represent loss.

Results

The characteristics of the study population are listed in Table 1. Subjects in the follow-up study of ultrasound parameters were approximately 4 years younger than the total population of the Rotterdam Study. They were less likely to report a history of non-vertebral fractures in the preceding 5 years and they were less disabled [3]. Median follow-up time between the first and second ultrasound measurements was 1.4 years (range 1.0–2.0 years). Follow-up time was similar for men and women. For SOS there was a significant and substantial decline per year in both sexes of −2.5 m/s (Table 1). There was no difference in the rates of change between men and women. For Stiffness the annual decline was −0.62 in men and −0.66 in women. For BUA, the longitudinally estimated rate of change was not significantly different from zero for both men and women. For SOS and BUA, but not for Stiffness, the longitudinally estimated rates of loss differed considerably from those estimated cross-sectionally, being most pronounced for SOS in men (Table 1). Mean rates of change for BMD varied between −0.002 (femoral neck) and −0.004 (Ward's triangle) g/cm^2 per year in women and between 0.003 (Ward's triangle) and 0.012 (femoral neck) g/cm^2 per year in men.

In men, but not in women, the rate of change in SOS and Stiffness tended to increase with age (Fig. 2). For SOS this trend was statistically significant in men only if subjects older than 80 years (who are more likely to be subject to selection bias) were excluded from the analysis [men: $\beta = -0.26$ m/s per $year^2$ (−0.50 to −0.02); women: $\beta = -0.06$ m/s per $year^2$ (−0.25 to 0.12)]. Rates of change for BUA were not significantly influenced by age in either sex, while body mass index, years since menopause and disability measured at baseline did not significantly influence the rates of change for either SOS or BUA, The correlation between the rates of change for SOS and BUA was low (R = 0.1, p = 0.014). No statistically significant correlation was observed between the rates of change for bone mineral density and either ultrasound parameter. As Stiffness is calculated from SOS and BUA values, it was not surprising to find a strong but meaningless correlation between Stiffness and SOS and between Stiffness and BUA.

For both SOS and BUA there was a substantial variation in the rate of change. With a median follow-up time of 1.4 years, approximately 27% of this variation in rates of change in SOS could be explained by measurement error. For BUA this percentage was 9% and for Stiffness it was 11%. Table 2 shows for SOS, Stiffness and BUA the percentage of subjects that had changes more than could be accounted for by measurement error. Figure 3 shows the estimated number of years necessary to conclude that the direction of a

Table 1. Baseline and follow-up characteristics

	Men (n=224)		Women (n=323)	
	Mean	(95% CI)	Mean	(95% CI)
Age (years)	66.5	(65.5 to 67.5)	67.3	(66.4 to 68.3)
Body mass index (kg/m^2)	25.7	(25.3 to 26.0)	26.5	(26.1 to 26.9)
SOS-1 (m/s)	1536	(1532 to 1540)	1515	(1511 to 1518)
SOS-2 (m/s)	1532	(1528 to 1537)	1511	(1508 to 1515)
Δ-SOS (m/s/year)	−2.5	(−4.0 to −1.1)	−2.5	(−3.6 to −1.4)
% Δ-SOS (%/year)	−1.9	(−3.0 to −0.8)	−2.2	(−3.2 to −1.2)
Cross-sectional (m/s per year)	−0.7	(−1.2 to −0.1)	−1.6	(−1.9 to −1.2)
BUA-1 (dB/MHz)	116.5	(115.1 to 117.9)	106.0	(104.7 to 107.3)
BUA-2 (dB/MHz)	116.6	(115.1 to 118.0)	106.0	(104.7 to 107.3)
Δ-BUA (dB/MHz/year)	0.11	(−0.64 to 0.87)	0.05	(−0.67 to 0.77)
% Δ-BUA (%/year)	0.09	(−0.55 to 0.75)	0.05	(−0.63 to 0.73)
Cross-sectional (dB/MHz/year)	−0.24	(−0.43 to −0.06)	−0.34	(−0.49 to −0.20)
Stiffness-1	87.6	(85.7 to 89.5)	74.8	(73.2 to 76.4)
Stiffness-2	86.7	(84.7 to 88.7)	73.8	(72.2 to 75.4)
Δ-Stiffness	−0.62	(−1.33 to −0.09)	−0.66	(−1.24 to −0.08)
% Δ-Stiffness	−0.71	(−1.53 to 0.10)	−0.89	(−1.67 to −0.11)
Cross-sectional	−0.35	(−0.60 to −0.09)	−0.66	(−0.83 to −0.49)

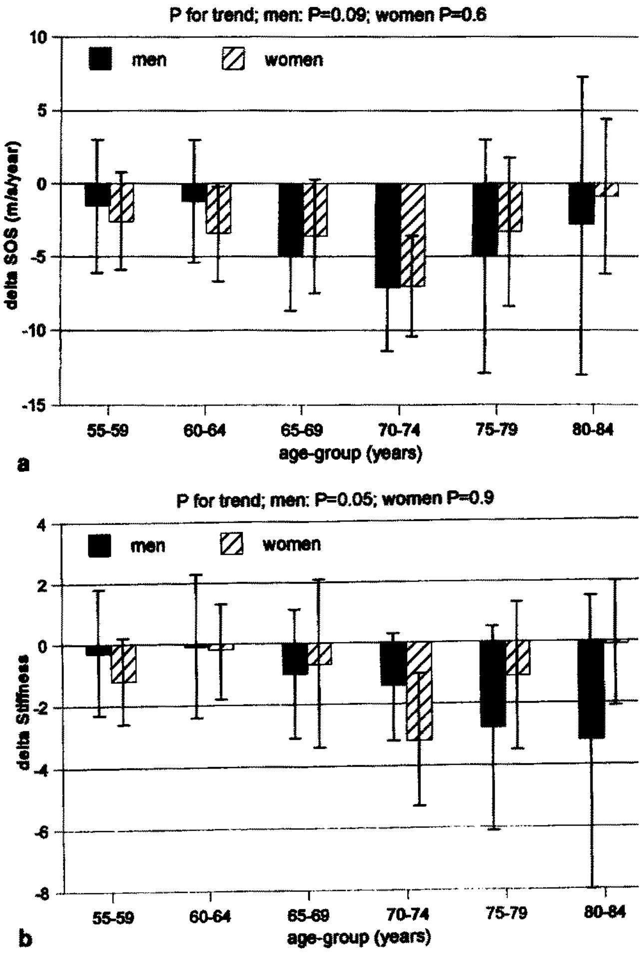

Fig. 2. Mean rate of change per year (95% CI) for SOS (**a**) and Stiffness (**b**) according to age group in men and women. *P* values are for linear trends.

Table 2. Percentage of subjects with a difference between the first and the second measurement larger than 2 standard deviations of the difference of two measurements performed on the same day (for SOS <15.3 m/s, for Stiffness <4.8, and for BUA <5.06 dB/MHz)

	Men	Women
SOS decrease	16.5%	13.8%
SOS increase	10.3%	7.8%
BUA decrease	13.8%	19.4%
BUA increase	14.7%	19.4%
Stiffness decrease	19.2%	21.0%
Stiffness increase	13.4%	14.1%

change in an individual is not attributable to measurement error. Although the direction of the change is unlikely to be due to measurement error for any change at the right-hand side of the curve, the exact magnitude of the change is still uncertain. For instance, if we find, after a follow-up of 4 years that a subject has a rate of loss of 10 m/s per year in SOS, this may easily vary between 6 and 14 m/s per year [(rate of loss per year × follow-up time ± 15.3)/follow-up time]. With increasing follow-up time this uncertainty will become smaller.

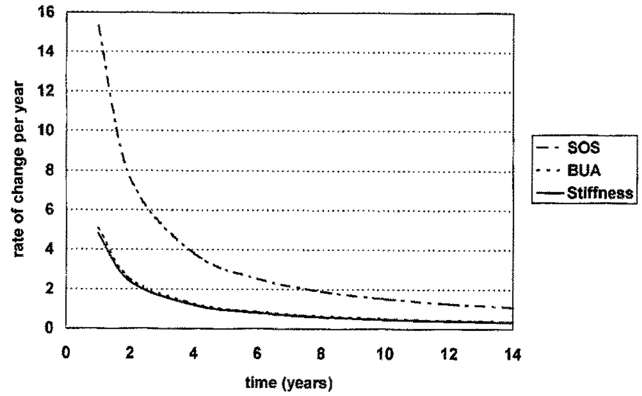

Fig. 3. Number of years necessary to state that the direction of a change in an individual is not attributable to measurement error. Curves are estimated using a coefficient of variation of 0.5% for SOS, 2.3% for BUA and 3.0% for Stiffness, with a mean value for SOS of 1530 m/s, for BUA of 110 dB/MHz and for Stiffness of 80.

Figure 3 also shows the relative value of a coefficient of variation, or rather its dependence on the minimum level of the parameter. Although the coefficient of variation is smaller for SOS than for BUA, it will take longer to conclude that a change of a certain magnitude and direction is true for SOS than for BUA. For this reason, it is better to use the standardized coefficient of variation when comparing the precision of various parameters.

Discussion

In the present study a significant decline in SOS (men and women) and Stiffness (women) was found after a relatively short follow-up of 1.4 years. For BUA no significant loss could be observed. Our findings may have been hampered by the fact that the subjects studied belong to a relatively healthy sample of the Rotterdam Study cohort. Nonetheless, the decrease in SOS and Stiffness per year was substantial in both sexes, and may, therefore, even be higher in the overall population.

Cross-sectional studies show that hip fracture risk more than doubles per standard deviation decrease in SOS [11,12]. A reduction in SOS of the magnitude found in our study may therefore be associated with an increase of around 15% in fracture risk per year. This appears to be of the same magnitude as the observed increase in hip fracture risk per year in The Netherlands [13].

Especially in men, the longitudinal changes in SOS are larger than those estimated from a cross-sectional analysis. Selection and survival bias or cohort effects may explain a difference between cross-sectional and longitudinal results. Non-response and mortality in the oldest age group will tend to reduce the apparent effect of age on SOS. Furthermore, with an increasing rate of change with age, especially this elderly group of subjects influences the mean rate of loss in a longitudinal analysis.

One would have expected to find a similarly higher rate of change in BUA as compared with cross-sectional data. Instead, there even was a tendency to an increase in BUA over time. Similar observations have been made by Krieg et al. [14] and Schott et al. [15]. The latter reported that the rate of change in SOS assessed longitudinally were 3.5–4.5 times higher than those calculated cross-sectionally, whereas the longitudinally assessed rates of change in BUA were similar to the ones from a cross-sectional analysis. The reason for this discrepancy is unclear. The fact that SOS and BUA reflect different aspects of bone may play a role. SOS is supposed to be related to the elastic properties of bone, whereas BUA is thought to reflect structural aspects of bone tissue [2].

The age-dependent increase in the rate of change of SOS and Stiffness in men is in agreement with the increased rate of change in bone mineral density with age that has been reported by Jones et al. [8]. However, we did not find a significant increase in the rate of change in ultrasound parameters with age in women. One has to bear in mind that although rates of change were assessed longitudinally, the analysis of rates of change with age is in fact cross-sectional, with the potential hazard of selection bias. Nevertheless, it is unlikely that selection bias will induce an increase in rates of change with age. Rather, selection of relatively healthy subjects in the older age groups, as may have been the case in the present study, will tend to decrease the rate of change with age. The difference in age-related rates of bone loss between men and women might be explained as follows. As can be seen in Fig. 2, the increase in the rate of change with age in men appears to start around the age of 65 years, which is approximately the time at which men retire in The Netherlands. Retirement might be related to a change in loading of the skeleton. We have recently shown that physical activity is an especially important determinant of SOS in men [3]. In contrast, women in this age group tend not to have outdoor jobs. Therefore, it is less likely that they will change their level of physical activity on retirement. On the other hand, if this were to be the explanation, one would have expected to find an association between baseline disability and rates of change.

Short-term precision of ultrasound measurements is reported to be very good [16,17]. Nonetheless, if the changes studied are small, even a measurement error of the size reported for SOS may seriously hamper the use of the measurement in the follow-up of individual patients. This is illustrated by the considerable part of the variation in the rates of change that can be attributed to measurement error. If follow-up time is short it will be almost impossible to judge what proportion of an observed change between two measurements is real and what proportion is due to measurement error [18,19]. A way to reduce this problem would be to repeat the measurements on the same day and take the average of the measurements. Overall, the average of the measurement will be closer to the true value and the measurement error will thereby be smaller. With increasing follow-up time, variability due to imprecision relative to true variability will become smaller. We may, therefore, be able to demonstrate small changes per year in an individual if the interval between two measurements is long, as was illustrated in Fig. 3.

Taken together, for SOS and Stiffness, but not for BUA, there is a significant change per year. Furthermore, in men there is an increasing rate of change in SOS and Stiffness with increasing age. Finally, the magnitude of the yearly changes in comparison with the precision of the measurements may limit the use of ultrasound measurements as a follow-up tool in individuals rather than in populations.

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References

1. Riggs BL, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;3:314:1676–86.
2. Hans D, Schott AM, Meunier PJ. Ultrasound assessment of bone: a review. Eur J Med 1993;2:157–63.
3. Van Daele PLA, Burger H, Algra D, et al. Age-associated changes in ultrasound measurements of the calcaneus in men and women: the Rotterdam study. J Bone Miner Res 1994;9:1751–7.
4. Baran DT, McCarthy CK, Leahey D, Lew R. Broadband ultrasound attenuation of the calcaneus predicts lumbar and femoral neck density in Caucasian women: a preliminary study. Osteoporosis Int 1991;1:110–3.
5. Waud CE, Lew R, Baran DT. The relationship between ultrasound and densitometric measurements of bone mass at the calcaneus in women. Calcif Tissue Int 1992;51:415–8.
6. Damilakis JE, Dretakis E, Gourtsoyiannis NC. Ultrasound attenuation of the calcaneus in the female population: normative data. Calcif Tissue Int 1992;51:180–3.
7. Burger H, Van Daele PLA, Algra D, et al. The association between age and bone mineral density in men and women aged 55 years and over: the Rotterdam study. Bone Miner 1994;25:1–13.
8. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. BMJ 1994;309:691–5.
9. Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly. Eur J Epidemiol 1991;7:403–22.
10. Miller CG, Herd RJ, Ramalingham T, Fogelman I, Blake GM. Ultrasonic velocity measurements through the calcaneus: which velocity should be measured? Osteoporosis Int 1993;3:31–5.
11. Schott AM, Weill-Engerer S, Hans D, Duboeuf F, Delmas PD, Meunier PJ. Ultrasound discriminates patients with hip fracture equally well as dual energy x-ray absorptiometry and independently of bone mineral density. J Bone Miner Res 1995;10:243–9.
12. Hans D, Dargent P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fractures in elderly women: the Epidos prospective study. Lancet 1996;348:511–4.
13. Ooms ME, Vlasman P, Lips P, Nauta J, Bouter LM, Valkenburg HA. The incidence of hip fractures in independent and institutionalized elderly people. Osteoporosis Int 1994;4:6–10.
14. Krieg MA, Thiébaud D, Burckhardt P. Quantitative ultrasound of bone in institutionalized elderly women: a cross-sectional and longitudinal study. Osteoporosis Int 1996;6:189–95.
15. Schott AM, Hans D, Garnero P, Sornay-Rendu E, Delmas PD, Meunier PJ. Age-related changes in os calcis ultrasonic indices: a 2-year prospective study. Osteoporosis Int 1995;5:478–83.
16. Schott AM, Hans D, Sornay-Rendu E, Delmas PD, Meunier PJ.

Ultrasound assessment of os calcis precision and age-related changes in a normal female population. Osteoporosis Int 1993;3:249–54.
17. Wüster C. Bone density measurement of calcaneus with ultrasound: a new precision procedure with good agreement to vertebral measurement. Osteologie 1992;1(Suppl 1): 85.
18. Kanis JA. Problems in design of clinical trials in osteoporosis. In: J, Dixon A, Russell RGG, Stamp TCB (eds). Osteoporosis: a multidisciplinary problem. R Soc Med Int Cong Symp Series 55:205–222
19. Davis JW, Ross PD, Wasnich RD, Maclean CJ, Vogel JM. Comparison of cross-sectional and longitudinal measurements of age-related changes in bone mineral content. J Bone Miner Res 1989;4:351–7.

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