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Peripheral quantitative computed tomography measures are associated with adult fracture risk: The Hertfordshire Cohort Study

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ABSTRACT

Peripheral quantitative computed tomography (pQCT) captures novel aspects of bone geometry that may contribute to fracture risk and offers the ability to measure both volumetric bone mineral density (vBMD) and a separation of trabecular and cortical compartments of bone, but longitudinal data relating measures obtained from this technique to incident fractures are lacking. Here we report an analysis from the Hertfordshire Cohort Study, where we were able to study associations between measures obtained from pQCT and DXA in 182 men and 202 women aged 60–75 years at baseline with incident fractures over 6 years later. Among women, radial cortical thickness (HR 1.72, 95% CI 1.16, 2.54, $p = 0.007$) and cortical area (HR 1.91, 95% CI 1.27, 2.85, $p = 0.002$) at the 66% slice were both associated with incident fractures; these results remained significant after adjustment for confounders (age, BMI, social class, cigarette smoking and alcohol consumption, physical activity, dietary calcium, HRT and years since menopause). Further adjustment for aBMD made a little difference to the results. At the tibia, cortical area (HR 1.58, 95% CI 1.10, 2.28, $p = 0.01$), thickness (HR 1.49, 95% CI 1.08, 2.07, $p = 0.02$) and density (HR 1.64, 95% CI 1.18, 2.26, $p = 0.003$) at the 38% site were all associated with incident fractures with the cortical area and density relationships remaining robust to adjustment for the confounders listed above. Further adjustment for aBMD at this site did lead to attenuation of relationships. Among men, tibial stress–strain index (SSI) was predictive of incident fractures (HR 2.30, 95% CI 1.28, 4.13, $p = 0.005$). Adjustment for confounding variables and aBMD did not render this association non-significant. In conclusion, we have demonstrated relationships between measures of bone size, density and strength obtained by pQCT and incident fracture. These relationships were attenuated but in some cases remained significant after adjustment for BMD measures obtained by DXA, suggesting that some additional information may be conferred by this assessment.

Introduction

In recent years, new techniques to assess bone strength have been developed, but longitudinal data relating measures obtained from these techniques to incident fractures are lacking [1]. One such technique is peripheral quantitative computed tomography (pQCT) [2]. This technique was introduced some years ago as a method for assessing volumetric bone mineral density (vBMD). This technique confers little risk to the individual because exposure to radiation occurs only at a localised, peripheral site and captures aspects of bone geometry that may contribute to fracture risk such as apparent trabecular bone structure. It also offers the ability to measure volumetric bone mineral density (vBMD) and can estimate trabecular and cortical compartments of bone. This is of particular interest as it has been suggested that alterations of cortical and trabecular structure are differentially associated with fragility fractures in postmenopausal women [3]. Case control studies using QCT techniques have highlighted differences in bone architecture and vBMD between individuals with or without fractures [4–7] but while results from pQCT of the forearm using single slice acquisition protocols have been shown to differentiate between cases and controls in studies of hip fractures in post-menopausal women, results are mixed with some reporting and some failing to report differences [8–13]. Furthermore, only one study has reported relationships between pQCT measures and fracture risk in men [14].

Further information about any clinical utility of this technology would therefore be helpful. Here we present results from the Hertfordshire Cohort Study (HCS), where we studied associations between measures obtained at multiple slices of the radius and tibia from pQCT, with incident fracture. Participants in the HCS were all born in Hertfordshire between 1931 and 1939, and at the time of the baseline visit for this study (in 2005–2006), were of mean age 69 years.

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Materials and methods

In the late 1990s, 1579 men and 1413 women aged 60–75 years were recruited to a study, which was designed to examine the relationship between growth in infancy and the subsequent risk of adult disease, including osteoporosis (the Hertfordshire Cohort Study). The selection procedure for these individuals was as follows: in brief, with the help of the National Health Service Central Registry at Southport and Hertfordshire Family Health Service Association, we traced men and women who were born during 1931–1939 in Hertfordshire using the NHSCR, and still lived there during the period 1998–2003 [15]. Different geographic clusters of this cohort have participated in waves of clinical investigation over the periods 1998–2003; 2005–2006; and 2011–2012.

During the initial wave, a detailed lifestyle questionnaire was administered to all participants to obtain information regarding medical history and lifestyle. Habitual activity was derived as a standardised score ranging from 0 to 100 for frequency of gardening, housework, climbing stairs and carrying loads in a typical week. Higher scores indicate a greater level of activity. Dietary calcium intake was calculated from a food frequency questionnaire. A drug history was taken; participants taking bisphosphonates were excluded, although women taking hormone replacement therapy were included in the study. Social class was identified on the basis of current or most recent full-time occupation for men and never-married women, but on the basis of the husband's occupation for ever-married women.

In 2005–2006 a follow-up clinic visit was conducted among participants living in East Hertfordshire who had previously attended for a DXA scan. Bone density testing at baseline in the HCS had been offered only in East Hertfordshire, and 498 men and 468 women had undergone a DXA scan. Of these, in 2005–2006, 437 men and 447 women who were still alive and living in the geographical area of East Hertfordshire were invited for a follow-up study. Of these, 322 men (65%) and 320 women (68%) agreed to participate. Reasons for not wishing to participate were not sought. At this visit, a detailed lifestyle questionnaire was again administered. Height was measured to the nearest 1 cm using a Harpenden pocket stadiometer (Chasmors Ltd., London, UK) and weight to the nearest 0.1 kg on a SECA floor scale (Chasmors Ltd., London, UK). Body mass index (BMI) was calculated as weight divided by height^2 (kg/m^2). The radial length was measured from the medial aspect of the ulnar styloid process to the distal and the medial aspect of the olecranon process; the tibial length was measured from the prominence of the medial malleolus to the medial aspect of the tibial plateau.

Peripheral quantitative computed tomography was performed on 313 men and 318 women on the radius and tibia (non-dominant side) using a Stratec XCT2000 instrument. The voxel size was 500 μm, scan speed 20 mm/s and slice thickness 2.4 mm. The X-ray current was 0.192 mA and the voltage was 58 kV. A scout view was performed on the forearm and lower leg to identify anatomical landmarks for placement of a reference line to correctly identify the relative region of interest. The cortical endplates of the radius and tibia were identified by visual inspection of the scout view by an experienced technician and used as anatomical landmarks. The reference line was fixed at the distal aspect of the base of the radial inclination. A reference line was set at right angles to the long axis of the tibia, and then fixed to bisect the distal tibial endplate in a transverse plane. This was defined as the plateau portion of the distal tibia, positioned on the distal aspect of the cortical shell. Scans were then obtained at regions of interest equal to a percentage of the limb length measured from the distal to proximal direction. Two slices were taken in the radial scan (4% & 66%) and three slices were taken for assessment of bone structure in the lower leg scan (4%, 14%, 38%). Trabecular parameters were measured distally (4%) and cortical parameters more proximally (14%, 38% and 66%). Short-term measurement precision error, expressed as a root mean square coefficient of variation, ranged from 0.55% (total tibial density, 4% slice) to 6.02% (radius fracture load (x)), but was typically between 1 and 3%. These figures were obtained using images acquired from 20 volunteers who were part of the study and hence were representative of the study population. These subjects underwent 2 scans on the same day, with the study limb repositioned in the machine between examinations. The threshold for bone was set at 280 mg/cm^3 and the threshold for separating trabecular and cortical bone was 710 mg/cm^3. Bone strength was estimated with respect to torsion (polar strength strain index or SSI). All images were reviewed for motion grade by the research technician at the end of each clinic; a subjective decision to exclude unacceptable scans was made. Areal bone mineral density (aBMD) measurements of the lumbar spine and femoral neck were obtained contemporaneously (within a period of 3 months) using a Hologic QDR 4500 dual energy X-ray absorptiometer.

Incident fracture ascertainment

In 2011, 216 men and 221 women from East Hertfordshire participated in another follow-up study performed to further study musculoskeletal health in this group. Of the group that had undergone pQCT at baseline, 591 were still alive and living in Hertfordshire. Of this group, 443 agreed to participate; in the remainder, a reply to say that the subject was unwilling or unable to participate in this phase of the study was received from 105 potential participants; the remainder did not respond to the original invitation or a reminder letter. Subjects were visited at home by a research nurse who administered a questionnaire that included questions on any new fractures since the last clinic visit. Failure to participate in the follow-up study was due to deaths, participants moving from the area and participants withdrawing from the study. Personal self-report of fracture at any site was recorded on a questionnaire mannekin.

Data on incident fractures, all confounders and either a radial or tibial pQCT scan were available on 182 men and 202 women, and we confined analyses to this group.

The East and North Hertfordshire Ethical Committees granted ethical approval for the study and all participants gave written informed consent.

Statistical methods

Normality of variables was assessed by comparing histograms of the data with normal probability curves and by inspecting QQ plots and variables transformed as required. Standard deviation (SD) scores were calculated by subtracting the mean of a pQCT measure from each individual value and dividing by the standard deviation. Negative SD scores were derived by multiplying the SD score by -1. Cox's proportional hazard models were used to assess the associations between each pQCT measure and incident fracture with the results presented as hazard ratios for the incident fracture associated with a 1 SD reduction in each pQCT measure. Cox–Snell residuals were used to asses model fit by comparing a plot of their cumulative hazard with the slope of an exponential distribution with hazard ratio. A p-value of ≤ 0.05 was considered to be significant for all analyses. The Stata statistical software package (version 12) was used for analyses.

Results

The characteristics of the study population at baseline are displayed in Table 1. The flow of participants through the study is illustrated in Fig. 1. The mean age at follow-up was 75.5 (SD 2.5) years in men and 75.8 (SD 2.6) years in women.

Twenty seven women and 13 men reported a fracture occurring during the follow-up period after bone assessment by DXA and pQCT. The distribution of fracture was as follows: upper limb: men: 5, women: 12; clinical vertebral: men: 1, women: 2; hip: men: 0, women: 2; hand or foot: men: 3, women: 4; distal femur or tibia: men: 2, women: 6; other: men: 2, women: 1.