**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 (BMD) and a separation of trabecular and cortical compartments of bone, but longitudinal data relating measures obtained from this techniques to incident fracture are lacking. Here we report this analysis from the Hertfordshire Cohort Study, where we were able to study associations between measures obtained from pQCT in 182 men and 202 women with incident fracture some 6 years later in a population in their eighth decade. 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 fracture; these results remained significant after adjustment for lifestyle confounders (age, BMI, social class, cigarette smoking and alcohol consumption, physical activity, dietary calcium, HRT and years since menopause). Further adjustment for BMD made 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 fracture with the cortical area and density relationships remaining robust to adjustment for the confounders listed above. Further adjustment for BMD at this site, however, did lead to attenuation of relationships. Among men, tibial strength strain index (SSI) was predictive of incident fracture (HR 2.30, 95% CI 1.28, 4.13, p=0.005. Adjustment for confounding variables and BMD did not remove this association. In conclusion, we have found associations between pQCT cortical and size measures with incident fracture that were attenuated but often remained after adjustment for BMD; these associations were generally stronger in females than males.

Keywords: bone; epidemiology; fracture

#### Introduction

In recent years, new techniques to assess bone strength have been developed, but longitudinal data relating measures obtained from these techniques to incident fracture 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 (BMD). It involves a low radiation dose, captures aspects of bone geometry that may contribute to fracture risk such as bone strength and geometry and offers the ability to measure both volumetric BMD and a separation of trabecular and cortical compartments of bone, an ability that 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]. While pQCT of the forearm at the ultra-distal radius using single level scanners has been shown in some studies to predict hip fractures in post-menopausal women, results are conflicting [4-9] and only one study has reported relationships between pQCT measures and fracture risk in men [10]. A need for studies using multilevel scanners in further populations, especially those that allow assessment of fracture prediction in longitudinal surveys, has also been highlighted and for this reason we report this analysis from the Hertfordshire Cohort Study, where we were able to study associations between measures obtained from pQCT with incident fracture in a population in their eighth decade.

**Materials and Methods**

In the late 1990s, 3000 men and 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 1931-39 in Hertfordshire, and still lived there during the period 1998-2003 [11]. The birth weight and weight at one year of age of each individual had been recorded in a ledger by a team of midwives and health visitors who had attended each birth in Hertfordshire in the 1930s and visited the child’s home at intervals during the first year of life.

313 men and 318 women participated in a study of musculo-skeletal health that included a pQCT scan. At a clinic visit, a detailed lifestyle questionnaire was administered to obtain information regarding medical history and lifestyle (including cigarette smoking and alcohol consumption). Habitual activity was derived as a standardised score ranging 0-100 from frequency of gardening, housework, climbing stairs and carrying loads in a typical week. Higher scores indicate a greater level of activity. Social class was identified on the basis of own 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.Height was measured to the nearest 0.1cm using a Harpenden pocket stadiometer (Chasmors Ltd, London, UK) and weight to the nearest 0.1kg on a SECA floor scale (Chasmors Ltd, London, UK). Body mass index (BMI) was calculated as weight divided by height2 (kg/m2). The radial length was measured from the distal end of the ulna styloid to the tip of the olecranon in mm; the tibial length was measured from the prominence of the medial malleolus to the tibial plate in mm.

Peripheral quantitative computed tomography (pQCT) was performed of the radius and tibia (non-dominant side) using a Stratec 2000 instrument. A scout view was performed on the forearm and lower leg to identify a baseline for the measurements. The cortical end plate of the radius was used as an anatomical landmark. The reference line was fixed in the lateral, horizontal part of the radial cortical end plate. The middle of the distal cortical end of the tibia was used as a reference line. Two slices were taken in the forearm scan (4% & 66%); four slices were taken for the lower leg scan (4%, 14%, 38%, 66%). Measurement precision error, expressed as a coefficient of variation, ranged from 0.88% (tibial total density, 4% slice) to 8.8% (total radial area, 66% slice), but was typically around 1-3%. These figures were obtained by 20 volunteers who were part of the study undergoing 2 scans on the same day, the limb repositioned in the machine between examinations. The threshold for bone was set at 280mg/cm3. Bone strength was estimated with respect to torsion (polar strength strain index or SSI). Measurements were made at 2 sites in the radius (4% and 66% slice) and in the tibia (4% and 38% slice). Bone mineral density measurements of the lumbar spine and femoral neck were obtained contemporaneously using a Hologic QDR 4500 instrument.

## Incident fracture ascertainment

In 2011, 216 men and 221 women participated in a follow-up study performed to ascertain musculoskeletal health in this group. Subjects were visited at home by a research nurse who administered a questionnaire that included questions on any incident fracture since the last clinic visit.

Full data on all variables were available on 182 men and 202 women.

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 and variables transformed as required. Cox’s proportional hazards models were used to estimate the hazard ratio for the incident fracture risk associated with a 1 SD reduction in each pQCT measure.

###  The Stata statistical software package (version 12) was used for the analyses.

# Results

The characteristics of the study population at baseline are displayed in Table 1. The mean age of the men and women studied was 69.1 and 69.4 years respectively.  The mean BMI was 26.8 and 27.1 in men and women respectively. The mean daily dietary calcium intake was 1191 mg and 1096 mg in men and women respectively. Forty percent of the men and 67 percent of the women had never smoked, while 8% of the men and 4% of the women were current smokers. The median alcohol consumption was 9.0 units (IQR 2.0 – 16.8) in men and 1.5 (IQR 0.0 – 4.5) in women. Twenty seven women and 13 men reported an incident fracture following bone assessment by DXA and pQCT.

Tables 2 and 3 show relationships between bone parameters obtained from the pQCT scan and incident fracture in males and females respectively. 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 fracture; these results remained significant after adjustment for lifestyle confounders (age, BMI, social class, cigarette smoking and alcohol consumption, physical activity, dietary calcium, HRT and years since menopause). Further adjustment for BMD made little difference to the results for cortical area. 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 fracture with the cortical area and density relationships remaining robust to adjustment for the confounders listed above. Further adjustment for BMD at this site, however, did lead to attenuation of relationships. Among men, tibial SSI was predictive of incident fracture (HR 2.30, 95% CI 1.28, 4.13, p=0.005). Adjustment for confounding variables and BMD did not remove this association.

Figure 1 highlights the consistently lower cortical parameters of thickness, area and density in both the radius and tibia of women that subsequently fractured. In men, differences in cortical parameters between fracture and non-fracture cases were inconsistent in both the upper or lower limbs.

# Discussion

We have shown that measures of bone density and strength as assessed by pQCT are associated with fracture, particularly among women; it is unclear whether the weaker relationships observed in men reflect limited power due to small number of fractures, or a true sex difference. We also found that relationships between pQCT measures and fractures generally remained after adjustment for BMD, suggesting that these measures of bone mass and strength do contribute some additional information regarding fracture risk.

This study has a number of limitations, the most significant of which is the small number of fractures among men, limiting our ability to draw conclusions in males. Ideally, we would wish to further characterise fracture according to site, but numbers did not allow this, even in women (where the majority of fractures reported were at the radius). The individuals recruited were selected because they had been born in Hertfordshire, and continued to live there at the age of 60-75 years, as in previous studies. However, we have previously demonstrated that the Hertfordshire populations studied have similar smoking characteristics and bone density to national figures [12], suggesting that selection bias is minimal.

QCT has been use at other sites to predict fracture; hence, in the EFFECT study, a case control study of hip fracture, DXA and QCT was performed. In this group, the researchers found that the best predictors of trochanteric fractures were trabecular BMD and cortical thickness of the trochanter; the predictive power of the two techniques was not significantly different [13]. Other groups have performed case control studies of vertebral compression fracture and confirmed lower volumetric BMD as assessed by QCT in fractures subjects [14].

We obtained pQCT data at the radius and tibia. Literature relating pQCT measures at these sites to bone bending strength have generally observed relationships between the two, but found the relationship attenuated by adjustment for BMD [15-17]. However, in clinical studies where pQCT measures have been related to fracture risk, an additional value of pQCT has recently been demonstrated. Hence in a recent publication from the MrOS [10] where 39 fractures were observed in a group of 1143 men aged 69 years or older, principal components analysis was used to identify 21 of 58 pQCT variables associated with incident fracture; of these variables, 18 still contributed to fracture risk, with AUC increasing from 0.73 to 0.80 with their inclusion. These observations may suggest that the weaker associations seen in men in our study do reflect power issues, rather than a genuine sexual dimorphism. However, of interest, tibial SSI was associated with incident fracture in this population, with a 13% difference observed in mean values between men who did and did not fracture over follow-up.

Other studies have suggested that trabecular and total BMD of the ultra-distal radius as determined by single slice QCT can be used to predict hip fractures, with an average age-adjusted standardised risk gradient of 1.85 for trabecular BMD and 1.75 for total BMD [4-7]. However, even fewer data are available for the prediction of vertebral fractures; two negative studies were conducted in US subjects [5,18] while the study that displayed a significant discriminatory capability for vertebral fractures was done in the UK [4]. Hence the ISCD has adopted a stance that the use of this technique is not advisable for the prediction of vertebral fractures, and has highlighted the need for other studies, such as our own [19].

Cancellous bone accounts for approximately 15% of total bone mass; vertebrae and pelvic bones contain relatively high amounts of cancellous tissue, and are common sites for osteoporotic fractures, whereas long bones such as the femoral neck contain a relatively high amount of cortical bone. Although about 70% of the variation in compressive strength of bone is determined by BMD [20], prediction of trabecular bone strength may be greatly improved by including other measures of bone quality; bone strength is also dependent upon other factors such as trabecular connectivity, elasticity, stress/ strain response, and failure point, in addition to bone size, shape, turnover and architecture [20]. Our results suggest that pQCT captures some of these elements, and offer an additional contribution to estimation of individual fracture risk.

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 often remained significant after adjustment for BMD measures obtained by DXA, suggesting that some additional information may be conferred by this assessment. They were also more apparent for cortical, rather than trabecular measures. These data supplement previous studies that have demonstrated differences between pQCT variables among case-control studies of fractured - non-fractured subjects. While sex differences were observed in the relationship between pQCT measures and fracture prediction, this is likely to represent limited power in this sample due to the low number of men sustaining a fracture over the follow-up period; in general relationships were stronger in women than men, although relationships were more marked with tibial measures in males . Of interest, tibial polar strength strain index was a predictor of fracture in our population, as it was in the MrOS Study, highlighting the utility of this measure. Further work in groups with higher numbers of incident fractures is now indicated.

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EMD and CC made substantial contributions to the conception and design of the study. EMD and CC were involved in data acquisition. EMD drafted the manuscript with input from ME, AAS, and CC. Statistical analysis was performed by KAJ. All authors contributed to the analysis and interpretation of the data, revised the manuscript critically for important intellectual content, and approved the final version of the submitted manuscript. EMD accepts responsibility for the integrity of the data analysis.

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**Table I Summary characteristics of study participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CharacteristicMean (SD) unless stated otherwise |  | **Males (n=182)** |  | **Females (n=202)** |  |
| Age (yrs) |  | 69.1 (2.5) |  | 69.4 (2.7) |  |
| BMI (kg/m2) a |  | 26.8 (1.1) |  | 27.1 (1.2) |  |
| Alcohol consumption (median (IQR) units per week) |  | 9.0 (2.0, 16.8) |  | 1.5 (0.0, 4.5) |  |
| Habitual activity (%)Dietary calcium intake (mg/day)a |  | 65.1 (13.9)1191 (1.3) |  | 62.4 (13.8)1096 (1.3) |  |
|  |  |  |  |  |  |
| N (%) Current manual social class (IIIM-V)b |  | 108 (59.3) |  | 110 (54.5) |  |
| N (%) Current non-manual social class (I-IIIN) b |  | 74 (40.7) |  | 92 (45.5) |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| N (%) Never smoked |  | 72 (39.6) |  | 136 (67.3) |  |
| N (%) Ex-smokerN (%) Current smoker |  | 95 (52.2)15 (8.2) |  | 58(28.7)8 (4.0) |  |
|  |  |  |  |  |  |

aGeometric mean (SD).

bI-IIIN and IIIM-V denote classes one to three (non-manual), and three (manual) to five, of the 1990 OPCS Standard Occupational Classification scheme for occupation and social class.

Table 2: Cox's proportional hazards models with pQCT variables as explanatory variables for incident fracture in men

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| pQCT variables (as negative SD scores) | Unadjusted |  | Adjusted for confounders1 |  | Adjusted for BMD and confounders2 |
| HR | 95% CI | p value | HR | 95% CI | p value | HR | 95% CI | p value |
| Radius |  |  |  |  |  |  |  |  |  |
| Total area, 4% slice (mm2)  | 0.93 | (0.52, 1.65) | 0.798 | 0.93 | (0.50, 1.73) | 0.820 | 10.93 | (0.50, 1.72) | 0.809 |
| Trabecular density, 4% slice (mg/cm3)  | 0.83 | (0.46, 1.50) | 0.544 | 0.84 | (0.44, 1.63) | 0.614 | 0.83 | (0.40, 1.74) | 0.621 |
| Cortical density, 66% slice (mg/cm3)  | 0.57 | (0.26, 1.22) | 0.146 | 0.46 | (0.20, 1.08) | 0.075 | **0.46** | **(0.20, 1.08)** | **0.047** |
| Cortical thickness, 66% (mm) | 0.86 | (0.45, 1.63) | 0.636 | 0.86 | (0.45, 1.66) | 0.656 | 0.86 | (0.42, 1.74) | 0.673 |
| Cortical area, 66% slice (mm2)  | 0.94 | (0.53, 1.66) | 0.829 | 1.00 | (0.55, 1.79) | 0.992 | 1.02 | (0.54, 1.92) | 0.961 |
| Total area, 66% slice (mm2)  | 1.04 | (0.66, 1.93) | 0.907 | 1.16 | (0.59, 2.26) | 0.668 | 1.17 | (0.60, 2.28) | 0.654 |
| Polar strength strain index, 66% slice (mm3) | 0.97 | (0.57, 1.67) | 0.919 | 1.03 | (0.59, 1.79) | 0.924 | 1.03 | (0.59, 1.82) | 0.905 |
|  |  |  |  |  |  |  |  |  |  |
| Tibia |  |  |  |  |  |  |  |  |  |
| Total area, 4% slice (mm2)  | 1.48 | (0.76, 2.87) | 0.246 | 1.46 | (0.74, 2.89) | 0.281 | 1.48 | (0.74, 2.93) | 0.266 |
| Trabecular density, 4% slice (mg/cm3)  | 0.85 | (0.51, 1.42) | 0.544 | 0.82 | (0.47, 1.44) | 0.488 | 0.76 | (0.44, 1.33) | 0.341 |
| Cortical density, 38% slice (mg/cm3)  | 0.63 | (0.32, 1.23) | 0.177 | 0.60 | (0.29, 1.25) | 0.174 | 0.55 | (0.26, 1.19) | 0.131 |
| Cortical thickness, 38% (mm) | 1.05 | (0.59, 1.89) | 0.862 | 0.99 | (0.53, 1.85) | 0.967 | 0.89 | (0.41, 1.93) | 0.7772 |
| Cortical area, 38% slice (mm2)  | 1.57 | (0.88, 2.79) | 0.124 | 1.59 | (0.85, 2.99) | 0.149 | 1.68 | (0.83, 3.42) | 0.151 |
| Total area, 38% slice (mm2)  | **2.12** | **(1.15, 3.91)** | **0.017** | 2.36 | (1.17, 4.75) | 0.016 | **2.37** | **(1.15, 4.87)** | **0.019** |
| Polar strength strain index, 38% slice (mm3)  | **2.30** | **(1.28, 4.13)** | **0.005** | **2.51** | **(1.31, 4.81)** | **0.006** | **2.79** | **(1.30, 5.97)** | **0.008** |

1 Adjusted for age, BMI, social class, smoker status, alcohol consumption, physical activity and dietary calcium

2 Adjusted for total femur BMD, age, BMI, social class, smoker status, alcohol consumption, physical activity and dietary calcium

Table 3: Cox's proportional hazards models with pQCT variables as explanatory variables for incident fracture in women

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| pQCT variables (as negative SD scores) | Unadjusted |  | Adjusted for confounders1 |  | Adjusted for BMD and confounders2 |
| HR | 95% CI | p value | HR | 95% CI | p value | HR | 95% CI | p value |
| Radius |  |  |  |  |  |  |  |  |  |
| Total area, 4% slice (mm2)  | 0.87 | (0.59, 1.28) | 0.484 | 1.06 | (0.69, 1.64) | 0.795 | 1.12 | (0.71, 1.75) | 0631 |
| Trabecular density, 4% slice (mg/cm3)  | 1.44 | (0.97, 2.12) | 0.068 | 1.43 | (0.90, 2.26) | 0.131 | 1.15 | (0.68, 1.94) | 0.608 |
| Cortical density, 66% slice (mg/cm3)  | 1.41 | (0.99, 2.01) | 0.059 | 1.31 | (0.88, 1.93) | 0.181 | 1.10 | (0.68, 1.71) | 0.676 |
| Cortical thickness, 66% (mm) | **1.72** | **(1.16, 2.54)** | **0.007** | **1.80** | **(1.12, 2.90)** | **0.016** | 1.50 | (0.87, 2.59) | 0.149 |
| Cortical area, 66% slice (mm2)  | **1.91** | **(1.27, 2.85)** | **0.002** | **2.20** | **(1.33, 3.65)** | **0.002** | **1.91** | **(1.04, 3.49)** | **0.036** |
| Total area, 66% slice (mm2)  | 1.24 | (0.80, 1.91) | 0.338 | 1.31 | (0.81, 2.12) | 0.278 | 1.27 | (0.78, 2.06) | 0.341 |
| Polar strength strain index, 66% slice (mm3) | 1.42 | (0.93, 2.17) | 0.102 | **1.54** | **(0.95, 2.48)** | **0.079** | 1.33 | (0.82, 2.16) | 0.241 |
|  |  |  |  |  |  |  |  |  |  |
| Tibia |  |  |  |  |  |  |  |  |  |
| Total area, 4% slice (mm2)  | 0.86 | (0.57, 1.29) | 0.467 | 0.94 | (0.61, 1.44) | 0.777 | 0.98 | (0.65, 1.48) | 0.921 |
| Trabecular density, 4% slice (mg/cm3)  | **1.69** | **(1.10, 2.60)** | **0.016** | 1.57 | (0.93, 2.64) | 0.090 | 1.17 | (0.65, 2.12) | 0.598 |
| Cortical density, 38% slice (mg/cm3)  | **1.64** | **(1.18, 2.26)** | **0.003** | **1.64** | **(1.10, 2.46)** | **0.016** | 1.39 | (0.89, 2.17) | 0.144 |
| Cortical thickness, 38% (mm) | **1.49** | **(1.08, 2.07)** | **0.015** | **1.34** | **(0.92, 196)** | **0.130** | 1.04 | (0.67, 1.61) | 0.860 |
| Cortical area, 38% slice (mm2)  | **1.58** | **(1.10, 2.28)** | **0.013** | **1.59** | **(1.05, 2.41)** | **0.030** | 1.27 | (0.80, 2.02) | 0.306 |
| Total area, 38% slice (mm2)  | 1.16 | (0.79, 1.71) | 0.459 | 1.37 | (0.89, 2.12) | 0.151 | 1.31 | (0.87, 1.98) | 0.199 |
| Polar strength strain index, 38% slice (mm3)  | 1.33 | (0.89, 1.99) | 0.162 | 1.54 | (0.98, 2.43) | 0.062 | 1.41 | (0.89, 2.23) | 0.138 |

1 Adjusted for age, BMI, social class, smoker status, alcohol consumption, physical activity, dietary calcium, HRT use and years since menopause

2 Adjusted for total femur BMD, age, BMI, social class, smoker status, alcohol consumption, physical activity, dietary calcium, HRT use and years since menopause

Figure 1: Mean difference in pQCT variables (negative SD score) between fracture and non-fracture cases in men and women.



Key: RCT = radial cortical thickness (66%); RCA = radial cortical area (66%); RCD = radial cortical density (66%); TCT = tibial cortical thickness (38%); TCA = tibial cortical area (38%); TCD = tibial cortical density (38%).