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ORIGINAL ARTICLE

Ischemic heart disease is associated with lower cortical volumetric bone mineral density of distal radius

J. Paccou[1,2] · M. H. Edwards[1] · K. A. Ward[3] · K. A. Jameson[1] · C. L. Moss[1] · N. C. Harvey[1] · E. M. Dennison[1,4] · C. Cooper[1,5,6]

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Abstract
Summary In this study, high-resolution peripheral quantitative computed tomography (HR-pQCT) was used to investigate geometric, volumetric and microstructural parameters at the distal radius and at the distal tibia in participants with ischaemic heart disease. We found that, compared with participants without ischaemic heart disease, they had substantially lower cortical volumetric bone mineral density (BMD) at the distal radius.
Introduction HR-pQCT captures novel aspects of bone geometry and volumetric bone mineral density (vBMD) and offers the ability to measure bone microarchitecture, but data relating measures obtained from this technique in patients with ischemic heart disease (IHD) are lacking.
Methods Here, we report an analysis from the Hertfordshire Cohort Study, where we were able to study associations between measures obtained from HR-pQCT of distal radius and distal tibia in 350 participants (184 men and 166 women) aged 71.5–80.5 years with or without IHD (e.g. heart attack, angina or heart failure; $n=75$ and $n=275$, respectively).
Results Analyses for all participants (men and women together) revealed that cortical vBMD (Ct.vBMD) was lower ($p<0.001$) and cortical thickness (Ct.th) was not different ($p=0.519$), whereas cortical porosity (Ct.Po) was higher ($p=0.016$) in participants with IHD at the distal radius. Moreover, trabecular microarchitectural parameters were not significantly different in patients with IHD ($p>0.05$ for all). Adjustment for a priori confounders (age, gender, body mass index, smoking status, alcohol consumption, high blood pressure and diabetes mellitus) did not materially affect the relationship described for Ct.vBMD ($p=0.002$), but differences in Ct.Po were attenuated. Analyses in men alone revealed that only Ct.vBMD was lower at the distal radius in participants with IHD with and without adjustment for a priori confounders ($p=0.0002$ and $p=0.004$, respectively), whereas no statistical differences were found in women, although patterns of differences were similar in both sexes. Moreover, no association was found between IHD and bone parameters at the distal tibia either in men or women.
Conclusions We have demonstrated that IHD is associated with lower Ct.vBMD of the distal radius.

Keywords Cortical porosity · Cortical volumetric bone mineral density · High-resolution peripheral quantitative computed tomography · Ischemic heart disease · Vascular calcification

✉ C. Cooper
cc@mrc.soton.ac.uk

[1] MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK

[2] Department of Rheumatology, Lille University Hospital, Lille 2, 59037 Lille cedex, France

[3] MRC Human Nutrition Research, Elsie Widdowson Laboratory, 120 Fulbourn Road, Cambridge CB1 9NL, UK

[4] Victoria University, Wellington, New Zealand

[5] NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford, Oxford OX3 5UG, UK

[6] NIHR Nutrition Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Trust, Southampton General Hospital, Southampton SO16 6YD, UK

Introduction

Cardiovascular disease (CVD), vascular calcification and osteoporosis are common in elderly individuals and have

previously been regarded as independent age-related disorders [1, 2]. However, some studies have suggested overlap in the etiological mechanisms of these diseases [3, 4]. For example, bone metabolism and vascular physiology share several regulatory factors, and the process of vascular calcification in many ways resembles that of bone formation [5, 6].

Furthermore, vascular calcification is both a marker and a cause of increased cardiovascular morbidity and mortality [7, 8]. Several studies showed that CVD and vascular calcification are associated with decreased bone mineral density (BMD) and increased bone fractures [9, 10]. Indeed, a diagnosis of CVD, either myocardial infarction, heart failure, stroke or peripheral arterial disease, has been shown to be related to the subsequent risk of osteoporotic fracture (mostly hip fracture) [11–14]. Although several studies exist on osteoporosis defined by densitometry, vascular calcification and CVD, the knowledge of bone microarchitecture in patients with CVD is still sparse.

The development of high-resolution peripheral quantitative computed tomography (HR-pQCT) has enabled us to investigate bone in greater detail [15]. Specifically, this evolving technique offers new possibilities to explore bone geometry, density and microstructure in patients with CVD and, to the best of our knowledge, this study is one of the first to do so. The aim therefore is to develop a better understanding in this area by investigating the relationships of bone geometry, volumetric BMD and bone microarchitecture with ischemic heart disease (IHD) and CVD in a well-phenotyped cohort of older men and women from Hertfordshire.

Methods

Study population

The Hertfordshire Cohort Study (HCS) is a population-based UK cohort which was designed to examine the relationships between growth in infancy and the subsequent risk of adult diseases, such as osteoporosis. Study design and recruitment have been described in detail previously [16]. In brief, in conjunction with the National Health Service Central Registry and the Hertfordshire Family Health Service Association, we traced men and women who were born between 1931 and 1939 in Hertfordshire and still lived there during the period 1998–2003. In 2011–2012, 570 men and women from the geographical area of East Hertfordshire were invited to take part in the study. Of these, 350 (61 %) agreed to both HR-pQCT scanning (distal radius and distal tibia) and a home visit which included a structured interview. The East and North Hertfordshire Ethical Committees granted ethical approval for the study, and all participants gave written informed consent in accordance with the Declaration of Helsinki [17].

Demographic and clinical assessment

A structured interview and physical examination were performed during a home visit. Demographics, clinical characteristics, traditional cardiovascular risk factors and history of CVD were collected. Specifically, the following characteristics were recorded: age, height (cm), weight (kg), smoker status and alcohol consumption. Height was measured to the nearest 0.1 cm using a wall-mounted SECA stadiometer on the day of scanning. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). History of fractures since 45 years old, diabetes mellitus or high blood pressure (HBP) was obtained through self-report. CVD included individuals who reported stroke, ischaemic heart disease (heart attack, angina or heart failure) or peripheral arterial disease (claudication). CVD, including IHD, was assessed by self-report, and assessment captures a lifetime history of disease. Concomitant drugs, such as insulin, β-blockers, calcium channel blockers, aspirin, clopidogrel, warfarin, statins, fibrates, biguanides and sulphonylureas, were also recorded.

High-resolution peripheral quantitative computed tomography

Each participant had measurements of the non-dominant distal radius and distal tibia using HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland) except when it had previously fractured in which case the dominant side was scanned. This allowed acquisition of a stack of parallel CT slices using a 2D detector array. A total of 110 slices were obtained which represented a volume of bone 9 mm in axial length with a nominal resolution (voxel size) of 82 μm. The scanned limb was immobilized during the examination in a carbon fibre cast. Antero-posterior 2D scout views were performed to determine the region to be scanned. All scans were acquired by one of two trained technicians using standard positioning techniques. These were in keeping with the manufacturer's guidelines and as described by Boutroy et al. [18]. Each scan was assessed for motion artefact, and if present, a second scan was performed. The quality of the measurements was assessed by using a 5-point scale recommended by the manufacturer (1, excellent; 2, good; 3, acceptable; 4, unacceptable; 5, poor) [19]. Only examinations with quality grades 1 through 3 were included in the study, whilst grades 4 and 5 were excluded. For this reason, 43 radius scans and 9 tibia scans were excluded.

Image analysis was carried out using the standard manufacturer's method which has been described in detail previously [20, 21]. In brief, we used a semi-automated, hand-drawn contouring system to delineate the periosteal surface. A threshold-based algorithm then separated cortical from trabecular compartments. The threshold used to discriminate cortical from trabecular bone was set to one third of the apparent

cortical bone density value. Standard morphologic analysis produced total (To.vBMD, g/cm^3) and trabecular BMD (Tb.vBMD, g/cm^3). Trabecular number (Tb.N, per mm) was determined using the ridge extraction method [22]. Trabecular thickness (Tb.Th, μm) and separation (Tb.Sp, μm) were calculated from trabecular density and trabecular number according to standard morphologic relationships [23]. Each measure has been validated against micro-CT imaging [24].

Further analysis was performed using an automated segmentation algorithm [25]. Assessments were made of total cross-sectional area (To.Area, mm^2), cortical area (Ct.Area, mm^2) and cortical density (Ct.vBMD, g/cm^3). Cortical density was determined as the average mineral density in the region of auto-segmentation cortical bone mask. Using Image Processing Language (IPL, version 6.1, ScancoMedical), cortical porosity (Ct.Po, %) was derived from the number of void voxels in each thresholded cortex image divided by the number of voxels in the cortex. Cortical thickness (Ct.Th, μm) was determined from the threshold cortex image using a distance transform after removal of intracortical pores [26]. Cortical pore diameter (Ct.Po.Dm, μm) was the mean 3D diameter of the intracortical pore space [27].

A calibration phantom (Scanco Medical AG, Bruttisellen, Switzerland) was used which included five cylinders containing a mixture of hydroxyapatite and resin. The mineral concentrations of these cylinders are 0, 100, 200, 400 and 800 mgHA/cm^3. The value of 0 mgHA/cm^3 equates to a soft tissue background devoid of mineral. Quality control testing was performed on a weekly basis and quality assurance on a daily basis. Short-term precision values (% CV) for cortical and trabecular BMD have been shown to range from 0.3 to 1.2 [28]. The effective dose to the subject during each scan was <3 μSv.

Statistical methods

Statistical analyses were performed using STATA version 13.1. Variables were assessed for normality and transformed if necessary. Descriptive statistics for continuous variables were expressed as mean, standard deviation or median, interquartile range (IQR), and categorical variables were expressed as frequency and percentage. Differences in continuous variables between participants with and without IHD and between genders were assessed using Student's *t* tests or Mann–Whitney tests and in categorical variables using Pearson's X^2 test or Fisher's exact test, as appropriate. Statistical significance was defined as a p value of ≤ 0.05.

Although there were differences in the values of bone and IHD variables between men and women, the relationships between them did not show any gender interactions. As a result, we presented results combined (with an adjustment for gender) and separately for the two genders. HR-pQCT measures were therefore described separately for men and women. Primary analysis used linear regression to examine the associations between IHD and HR-pQCT bone parameters in the distal radius and in the distal tibia. This analysis was undertaken with and without adjustment for a priori confounders: age, gender (if necessary), BMI, smoker status, alcohol consumption, HBP and diabetes mellitus. Secondary analysis used linear regression to examine the associations between any CVD (heart disease, stroke and peripheral arterial disease) and HR-pQCT bone parameters in the distal radius and in the distal tibia. This analysis was also completed with and without adjustment for a priori confounders: age, gender (if necessary), BMI, smoker status, alcohol consumption, HBP and diabetes mellitus. As multiple testing was carried out, this was taken into account using the Bonferroni correction. Thirdly, analyses used linear regression to examine separately the associations between several cardiovascular risk factors: diabetes mellitus (yes/no), HBP (yes/no), smoking status (ever/never) or current treatment by statins (yes/no) in men or women and HR-pQCT bone parameters in the distal radius and in the distal tibia. These analyses were undertaken with and without adjustment for age and BMI. Lastly, a logistic regression was used to examine the association between history of any fractures since 45 years old and IHD.

Results

Characteristics of study participants

Characteristics of the study participants are shown in Table 1. Participants with IHD (n=75) differed significantly in terms of age (IHD=76.3±2.5; controls=75.3±2.5 years), gender (males=64.0 % in IHD group and 49.5 % in control group) and weight (IHD=80.4±12.5; controls=76.6±13.9 kg) from those without IHD (n=250) though BMI was not statistically different. Concerning the prevalence of traditional cardiovascular risk factors, the two groups differed significantly in terms of HBP (IHD=66.7 %; controls=43.3 %) and diabetes (IHD=24.0 %; controls=9.8 %), but alcohol consumption and smoking status were not different. Concomitant drugs recorded (such as insulin, β-blockers, calcium channel blockers, aspirin, clopidogrel, warfarin, statins and biguanides) were all statistically most often prescribed in the IHD group (p<0.05 for all) except for sulphonylureas and fibrates. Stroke was reported in 17 participants, of whom seven did not have IHD. Peripheral arterial disease was reported in four individuals in total but in only one without IHD. A total of 83 (23.7 %) participants (53 men and 30 women) were classed as having CVD. A history of any fractures since 45 years old was reported in 85 (24.6 %) of the 346 participants (40 men and 45 women) for whom such data was available.

Table 1 Characteristics of study participants

Variables	All participants (n=350)	IHD (n=75)	Controls (n=275)	p value
Age, year	75.5±2.5	76.3±2.5	75.3±2.5	**0.003**
Male gender, n (%)	184 (52.6)	48 (64.0)	136 (49.5)	**0.025**
Body weight, kg	77.4±13.7	80.4±12.5	76.6±13.9	**0.031**
Body height, cm	167.1±9.1	168.6±9.4	166.6±9.0	0.099
BMI (kg/m^2)	27.7±4.2	28.3±4.1	27.5±4.3	0.150
Ever smoked, n (%)	171 (48.9)	39 (52.0)	132 (48.0)	0.539
Drink alcohol, n (%)	291 (83.1)	64 (85.3)	227 (82.6)	0.568
Drink consumption, unit per week Median [IQR]	3.1 [0.25-9.0]	4.5 [0.25-9.0]	3 [0.25-9.0]	0.700
HBP, n (%)	169 (48.3)	50 (66.7)	119 (43.3)	**<0.001**
Diabetes, n (%)	45 (12.9)	18 (24.0)	27 (9.8)	**0.001**
β-blockers, n (%)	67 (19.1)	37 (49.3)	30 (10.9)	**<0.001**
CC-blockers, n (%)	71 (20.3)	23 (30.7)	48 (17.5)	**0.012**
Aspirin, (%)	103 (29.4)	55 (73.3)	48 (17.5)	**<0.001**
Clopidogrel, n (%)	4 (1.1)	4 (5.3)	0	**0.002**
Warfarin, n (%)	25 (7.1)	12 (16.0)	13 (4.7)	**0.001**
Statins, n (%)	168 (48.0)	59 (78.7)	109 (39.6)	**<0.001**
Fibrates, n (%)	3 (0.9)	0	3 (1.1)	0.484
Insulin, n (%)	8 (2.3)	5 (6.7)	3 (1.1)	**0.013**
Biguanides, n (%)	21 (6.0)	9 (12.0)	12 (4.4)	**0.014**
Sulphonylureas, n (%)	12 (3.4)	4 (5.3)	8 (2.9)	0.295

Values are the mean±SD (significant results are indicated in bold)

BMI body mass index, *IHD* ischemic heart disease, *HBP* high blood pressure, *CC-blockers* calcium channel blockers

Bone geometry, volumetric BMD and microarchitecture

Regarding HR-pQCT bone variables from the distal radius in men and women, with the exception of Ct.vBMD (median (IQR): men=909.9 (881.4, 946.5); women=913.2 (871.2, 944.1)mg/cm^3) and Ct.Po.Dm (median (IQR): men=157.4 (150.8, 166.5); women=159.4 (150.1, 171.5)μm), bone geometry, cortical and trabecular microstructure differed significantly between men and women (p<0.001 for all parameters). Regarding HR-pQCT bone variables from the distal tibia in men and women, with the exception of Tb.Th (median (IQR): men=63.5 (57.0, 71.0); women=63.0 (54.0, 71.0)μm) and Ct.Po.Dm (median (IQR): men=176.2 (163.7, 188.3); women=178.9 (167.9, 190.1)μm) bone geometry, cortical and trabecular microstructure differed significantly between men and women (p<0.005 for all parameters).

Distal radial bone parameters in participants with and without IHD are shown in Table 2. Analyses for all participants (men and women together) revealed that Ct.vBMD was lower (β=−0.47 [−0.74, −0.21] Z-score; p<0.001); Ct.Th was not different, and Ct.Po was higher in patients with IHD (β=0.33 [0.06, 0.60] Z-score; p=0.016). Trabecular microarchitectural parameters were not statistically different. Adjustment for demographic, lifestyle covariates and cardiovascular risk factors (age, sex, BMI, smoker status, alcohol consumption, HBP and diabetes mellitus) did not materially affect the relationship described for Ct.vBMD (β=−0.45 [−0.72, −0.17] Z-score; p=0.002), but differences in Ct.Po were fully attenuated. Analyses in men alone revealed that only Ct.vBMD was lower in participants with IHD at the distal radius with and without adjustment for a priori confounders (β=−0.52 [−0.84, −0.20] Z-score; p=0.002 and β=−0.50 [−0.83, −0.16] Z-score; p=0.004, respectively), whereas no statistical differences were found in women, although patterns of differences were similar in both sexes. Differences in cortical bone microarchitecture at the distal radius are illustrated graphically in Fig. 1. The only result that remains significant, after multiple testing corrections, is the Ct.vBMD for all participants, unadjusted.

Moreover, when analyses were repeated comparing participants with and without CVD, the results were comparable (results not shown).

Analyses for all participants, in men alone and in women alone, did not find any association between bone parameters at the distal tibia assessed by HR-pQCT and history of IHD or CVD (results not shown).

After adjustment for age and BMI, distal radial bone parameter analyses in participants according to their smoker status, statin intake or history of diabetes revealed no significant differences amongst men or women. Analyses in men alone revealed that Tb.vBMD and Tb.Th were higher amongst

Table 2 Bone density and microstructure of distal radius in participants with ischemic heart disease and controls

Radius	All participants				Men				Women			
Variables	IHD	Controls	*p* value	*p* value[a]	IHD	Controls	*p* value	*p* value[b]	IHD	Controls	*p* value	*p* value[b]
To. area (mm^2)	367 (291, 440)	348 (280, 414)	0.100	0.683	426 (384, 474)	414 (381, 471)	0.652	0.441	280 (258, 306)	282 (259, 304)	0.964	0.776
Ct. area (mm^2)	59.9 (48.8, 69.6)	55.9 (45.7, 71.1)	0.468	0.242	67.4 (59.9, 75.6)	71.2 (62.0, 77.9)	0.125	0.156	46.4 (40.1, 53.1)	46.0 (41.3, 51.6)	0.599	0.971
Tb. area (mm^2)	292 (247, 372)	289 (232, 343)	0.067	0.381	352 (292, 408)	342 (308, 397)	0.337	0.183	231 (209, 262)	235 (206, 259)	0.995	0.820
Tb.vBMD (mg/cm^3)	164 (140, 199)	164 (138, 189)	0.771	0.562	179 (154, 200)	181 (160, 203)	0.563	0.484	146 (105, 162)	146 (110, 169)	0.759	0.959
Tb.N (per mm)	2.29 (2.09, 2.49)	2.28 (2.01, 2.44)	0.296	0.647	2.36 (2.21, 2.50)	2.37 (2.25, 2.50)	0.942	0.960	2.19 (1.97, 2.45)	2.12 (1.79, 2.34)	0.656	0.550
Tb.Th (μm)	60.0 (51.0 (68.0)	61.0 (54.0, 67.0)	0.551	0.161	63.0 (54.0, 69.0)	64.5 (59.0, 70.0)	0.580	0.439	51.0 (46.0, 60.0)	56.0 (51.0, 63.0)	0.157	0.255
Tb.Sp (μm)	379 (342, 419)	378 (344, 435)	0.363	0.824	259 (334, 396)	357 (334, 384)	0.895	0.838	404 (356, 464)	413 (372, 508)	0.719	0.583
Ct.vBMD (mg/cm^3)	**892 (851, 926)**	**915 (882, 948)**	**<0.001[c]**	**0.002**	**887 (851, 926)**	**912 (886, 952)**	**0.002**	**0.004**	901 (851, 928)	916 (874, 945)	0.071	0.072
Ct.Th (μm)	723 (630, 820)	754 (619, 875)	0.519	0.077	750 (685, 882)	825 (730, 927)	0.066	0.057	690 (567, 759)	685 (569, 770)	0.969	0.662
Ct.Po (%)	**3.88 (3.18, 4.69)**	**3.66 (2.60, 4.68)**	**0.016**	0.160	3.93 (3.32, 5.17)	3.94 (3.05, 4.85)	0.189	0.414	3.83 (3.16, 4.36)	3.31 (2.38, 4.29)	0.104	0.192
Ct.Po.Dm (μm)	158 (150, 167)	159 (151, 169)	0.955	0.581	158 (150, 164)	157 (151, 167)	0.879	0.433	156 (148, 168)	159 (152, 173)	0.849	0.837

Values are the median (IQR) (significant results are indicated in bold). *P* values are from linear regression analyses

IHD ischemic heart disease, *To.Area* total area, *Ct.Area* cortical area, *Tb.Area* trabecular area, *Tb.vBMD* trabecular volumetric bone mineral density, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Ct.vBMD* cortical volumetric bone mineral density, *Ct.Th* cortical thickness, *Ct.Po* cortical porosity, *Ct.Po.Dm* cortical pore diameter

[a] Adjusted for sex, age, BMI, smoking, alcohol, high blood pressure and diabetes

[b] Adjusted forage, BMI, smoking, alcohol, high blood pressure and diabetes

[c] Remains significant after correction for multiple testing (Bonferroni)

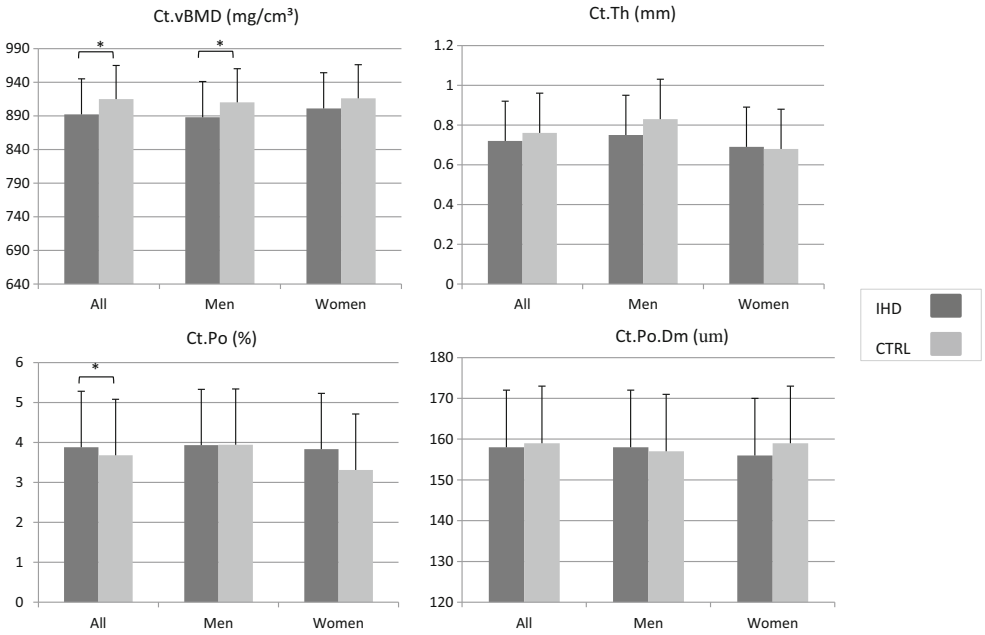

Fig. 1 Comparative analysis of cortical bone vBMD and microstructure in patients with heart disease (HD) and controls

participants with HBP (β=0.29 [0.03, 0.55] Z-score; p=0.030 and β=0.32 [0.04, 0.60] Z-score; p=0.027, respectively). Adjustment for age and BMI attenuated this relationship for Tb.vBMD but not for Tb.Th. Analyses in women alone revealed that Ct.Area, Ct.Th and Ct.Po.Dm were higher amongst participants with HBP after adjustment for age and BMI (β=0.25 [0.05, 0.45] Z-score; p=0.017, β=0.40 [0.11, 0.68] Z-score; p=0.007 and β=0.43 [0.07, 0.80] Z-score; p=0.021, respectively).

After adjustment for age and BMI, distal tibial bone parameter analyses in participants according to their smoker status or history of diabetes revealed no significant differences amongst men or women except higher Tb.vBMD in women with history of diabetes (β=0.52 [0.00, 1.03] Z-score; p=0.048). Analyses in men alone revealed that Tb.vBMD and Tb.Th were higher amongst participants with statin intake (β=0.36 [0.10, 0.62] Z-score; p=0.007 and β=0.29 [0.02, 0.55] Z-score; p=0.036, respectively), whereas Ct.vBMD was lower amongst men with HBP (β=−0.30 [−0.59, −0.01] Z-score; p=0.043).

Analysis by logistic regression failed to find any significant association between IHD and history of fractures (p=0.984).

Discussion

In this study, we utilized HR-pQCT to investigate geometric, volumetric and microstructural parameters at the distal radius and the distal tibia in participants with IHD in a cohort of older men and women from Hertfordshire. We found that, compared with participants without IHD, they had substantially lower Ct.vBMD and higher Ct.Po at the distal radius. Adjustment for a priori confounders did not materially affect the relationship for Ct.vBMD, but differences in Ct.Po were attenuated.

It is important to note that this is the first time that HR-pQCT has been used to assess the relationship between bone parameters and cardiovascular disease (self-reported IHD in our study) in a cohort of older men and women without end-stage renal disease. Moreover, our findings about lower Ct.vBMD at the distal radius in participants with IHD are of significant interest.

There are very few studies that have completed similar analyses. When volumetric BMD was assessed by peripheral QCT, cross-sectional data obtained in two studies involving only men found that ‘heart disease’ (defined by ‘myocardial infarction’ for the first study and by ‘cardiovascular disease’ for the second) was not related to trabecular or cortical BMD in either the radius or tibia [29, 30]. The most similar study to ours that utilized HR-pQCT compared 66 patients with end-stage renal disease on chronic haemodialysis with and without coronary artery calcification (CAC). They found that those with CAC had lower cortical bone density and trabecular bone volume than those without [31]. The former finding is in keeping with our results.

Other pQCT studies have focussed on vascular calcification and bone health rather than IHD specifically. Lower trabecular vBMD was related to high abdominal aortic calcification (AAC), but not to CAC, in a biracial (black and white) cohort of healthy middle-aged women independent of age and shared risk factors between osteoporosis and CVD [32]. In a substudy of the Multi-Ethnic Study of Atherosclerosis, lower trabecular vBMD was related to high AAC in men and CAC in women [33]. An inverse association has also been demonstrated between vertebral volumetric BMD and vascular

calcification (AAC, CAC and carotid artery calcified plaques) in African American men and women with type 2 diabetes [34]. Several dual-energy X-ray absorptiometry (DXA) studies have shown that CVD and vascular calcification are associated with decreased BMD and increased fracture risk, although findings vary according to skeletal site and gender [35]. In our study, no association was found between IHD and history of any fractures probably due to a lack of power.

It is not fully understood why individuals with IHD may have deficiencies in the amount and quality of their cortical bone. The pattern of cortical changes is of outstanding interest because Ct.Po is higher, whereas no difference has been found for Ct.Po.Dm. This suggests that pore number may be higher. The mechanisms underlying this association therefore remain to be elucidated. Several local and systemic factors may play a role. Firstly, chronic changes in intraosseous vascularization secondary to atherosclerosis could induce decreased blood flow with bone remodelling abnormalities and demineralization [36]. The reason why bone remodelling abnormalities and demineralization have only been observed in the cortical compartment in our study is unknown. However, based on data from subtrochanteric bone sections obtained in a cross-sectional study, one explanation may be that most bone loss is cortical, not trabecular, and, after age 65 years, occurs mainly by intracortical rather than endocortical or trabecular remodelling [37]. It is also possible that the intracortical blood supply is more precarious and therefore vulnerable to insult.

Secondly, serum levels of sclerostin are reportedly associated with cardiovascular calcification in both dialyzed and non-dialyzed chronic kidney disease patients [38]. Moreover, recent immunostaining and quantitative real-time PCR studies have demonstrated that sclerostin is upregulated in calcified cardiovascular tissue (relative to non-calcified cardiovascular tissue), indicating a potential role for this protein in cardiovascular calcification [38] which may lead to coronary artery disease. It remains to be shown whether sclerostin in the vasculature exerts paracrine anti-mineralization effects similar to those observed in bone. Although higher sclerostin levels may play a role in vascular calcification, it remains to determine whether higher sclerostin levels are associated with an increased [39, 40] or a decreased risk of fracture [41]. Currently, measurement of serum sclerostin levels in older men and women, even in combination with BMD results, does not appear to be of clinical utility [42]. Dkk1 concentrations, another Wnt-pathway inhibitor, are likely to better explain the association between vascular calcification and bone loss [43].

Furthermore, elevated levels of C-reactive protein and inflammatory cytokines have also been associated with both CVD and fracture risk [44]. Intriguingly, increased concentrations of high-sensitivity C-reactive protein have been found to be associated with poorer trabecular microarchitecture in men [45]. Oxidative stress has also been associated with severe vascular calcification and low bone stiffness. Any or a combination of these factors might in part explain the link between IHD and lower Ct.vBMD. Another reason why participants (collectively and men alone) with IHD had lower radial Ct.vBMD may be that they exercise less.

A number of reports have documented decreased BMD and increased fracture risk in smokers [46, 47]. Bone microarchitecture has been assessed at the distal radius and tibia according to smoker status in 810 men aged 60 and older from the STRAMBO cohort [48]. In former smokers, bone microarchitecture was similar to that in never-smokers, whereas current smoking was associated, at both skeletal sites, with lower Tb.vBMD and lower Tb.N than never-smokers [48]. The reason for the lack of associations found in the current study is again most likely to be the result of limited power. As in our study, with the exception of higher Tb.vBMD at the distal tibia amongst women, Farr and colleagues [49] recently found that bone microarchitectural parameters at the distal radius and tibia (derived by HR-pQCT) did not differ significantly between women with and without diabetes. Similar results were found by Shu and colleagues [50]. To the best of our knowledge, there is no study about hypertension and HR-pQCT, and there are very few studies about hypertension and QCT [29, 30]. For Barbour et al. [29], hypertension in men was positively and independently associated with both cortical and trabecular vBMD, whereas no association was found by Sheu et al. [30] for men at both distal radius and tibia. Statins are drugs with seemingly multiple actions, for which a possible effect on bone mass has been pointed out. However, such an effect is still discussed, and conflicting results have been published in this regard [51]. This is the first study about statin use and bone microarchitecture, and we found trabecular abnormalities at the distal tibia in men. Further studies are necessary to explore potential relationships between cardiovascular risk factors and bone microarchitecture and to assess associations between peripheral arterial disease and tibial microarchitecture.

The strengths of our study include in a well-phenotyped large cohort of older men and women and adjustment for multiple confounders. This study also has some potential limitations. Based on the cross-sectional nature of this study design, causality cannot be established because we are unable to determine temporal relationships between the variables. Many of the variables were collected through self-report, so there was potential for recall bias resulting in misclassification. Our study did not include laboratory assessments, so we could not investigate how bone metabolism in participants with IHD might have been affected by lower 25-OH vitamin D levels, altered renal function and their relationships with bone density and microarchitecture. Another limitation of our study is the relatively small number of individuals with IHD. This limits the power of the study, particularly when the group is further divided into men and women for subanalyses. HR-pQCT data is restricted to the peripheral skeleton and does not provide a direct measure of bone quality at axial sites such as hip and

vertebrae which are more common sites of fragility fracture. Moreover, the spatial resolution of the image is approximately 130 μm, and consequently, structures less than 100 μm are not typically resolved from in vivo images. This is of great importance due to the fact that pores not resolved in the HR-pQCT image (<<80 μm), probably representing the majority of all pores, are only contributing to lower Ct.vBMD rather than changes in Ct.Po. This limitation may contribute to the higher statistical robustness of Ct.vBMD compared to Ct.Po. Lastly, the only result that remains significant after the multiple corrections is the Ct.vBMD at the distal radius for all, unadjusted.

In summary, this study shows lower cortical vBMD most likely reflecting a larger number of remodelling sites (pores) in cortical bone of the radius in individuals with IHD when compared to those without. This may confer a biomechanical disadvantage and predispose to bone fragility and fracture. Identification of the potential mechanisms, potentially acting on intracortical remodelling, is likely to improve our understanding of the pathogenesis of bone fragility in patients with IHD.

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