Journal of Biomechanics xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Distal skeletal tibia assessed by HR-pQCT is highly correlated with femoral and lumbar vertebra failure loads

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ARTICLE INFO

Article history:
Accepted 13 May 2017
Available online xxxx

Keywords:
HR-pQCT
Multi-site
Bone microarchitecture
Bone strength
Osteoporosis

ABSTRACT

Dual energy X-ray absorptiometry (DXA) is the standard for assessing fragility fracture risk using areal bone mineral density (aBMD), but only explains 60–70% of the variation in bone strength. High-resolution peripheral quantitative computed tomography (HR-pQCT) provides 3D-measures of bone microarchitecture and volumetric bone mineral density (vBMD), but only at the wrist and ankle. Finite element (FE) models can estimate bone strength with 86–95% precision. The purpose of this study is to determine how well vBMD and FE bone strength at the wrist and ankle relate to fracture strength at the hip and spine, and to compare these relationships with DXA measured directly at those axial sites. Cadaveric samples (radius, tibia, femur and L4 vertebra) were compared within the same body. The radius and tibia specimens were assessed using HR-pQCT to determine vBMD and FE failure load. aBMD from DXA was measured at the femur and L4 vertebra. The femur and L4 vertebra specimens were biomechanically tested to determine failure load. aBMD measures of the axial skeletal sites strongly correlated with the biomechanical strength for the L4 vertebra ($r = 0.77$) and proximal femur ($r = 0.89$). The radius correlated significantly with biomechanical strength of the L4 vertebra for vBMD ($r = 0.85$) and FE-derived strength ($r = 0.72$), but not with femur strength. vBMD at the tibia correlated significantly with femoral biomechanical strength ($r = 0.74$) and FE-estimated strength ($r = 0.83$), and vertebral biomechanical strength for vBMD ($r = 0.97$) and FE-estimated strength ($r = 0.91$). The higher correlations at the tibia compared to radius are likely due to the tibia's weight-bearing function.

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1. Introduction

Osteoporosis is a degenerative skeletal disease characterized by bone loss and increased fracture risk. The World Health Organization (WHO) defines a person as osteoporotic based on areal bone mineral density (aBMD) measurements by dual energy X-ray absorptiometry (DXA) (Kanis, 1994). While aBMD has been shown to be a predictor of fracture risk (Adams, 2013; Ammann and Rizzoli, 2003) over 50% of all fractures in the elderly occur in people below the treatment threshold for osteoporosis (Schuit et al., 2004; Stone et al., 2003). Part of the challenge is that bone strength is an important contributor to fracture risk, and it depends on several factors, of which bone mass and bone microarchitecture are important (Adams, 2013; van der Linden and Weinans, 2007). Even though aBMD explains approximately 60–70% of bone strength (Adams, 2013; Ammann and Rizzoli, 2003), this 2D technology is limited for fracture prediction.

High-resolution peripheral quantitative computed tomography (HR-pQCT) provides 3D bone microarchitecture (Cheung et al., 2013), and has been used to establish normative population data for age-related bone microarchitecture changes (Burt et al., 2016; MacDonald et al., 2011; Nishiyama et al., 2009), as well age-related changes in bone strength based on finite element (FE) modeling (Emerson et al., 2013; MacDonald et al., 2011; MacNeil and Boyd, 2007). FE models from HR-pQCT are well suited to characterize forearm fractures (Boutroy et al., 2008; Cohen et al., 2009; Melton et al., 2007; Nishiyama et al., 2013a, 2013b), especially because the radius is one of the sites it can measure directly. However, the broader challenge of HR-pQCT is that it cannot perform

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http://dx.doi.org/10.1016/j.jbiomech.2017.05.011
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Please cite this article in press as: Kroker, A., et al. Distal skeletal tibia assessed by HR-pQCT is highly correlated with femoral and lumbar vertebra failure loads. J. Biomech. (2017), http://dx.doi.org/10.1016/j.jbiomech.2017.05.011

direct measurements at the main sites for osteoporotic fracture, including the proximal femur and lumbar spine.

Efforts to relate the radius and tibia peripheral sites to the axial skeleton are based on the assumption that the skeleton undergoes systemic changes. Directly supporting this assumption, a study by Liu and colleagues (Liu et al., 2010) showed that volumetric bone mineral density (vBMD) of peripheral sites by HR-pQCT were correlated significantly with quantitative CT measures of axial sites based on vBMD and FE-based stiffness. These findings are important, but the limitation is that the gold-standard of axial skeletal strength is not image-based measures of vBMD or FE-estimated strength, but an actual biomechanical test. Bone strength is a fundamental component of fracture risk, yet it is not clear whether using advanced methods such as HR-pQCT at peripheral skeletal sites can be useful predictors for axial skeletal bone strength. Investigating this is of interest as previous work has shown that aBMD and bone mineral content (BMC) measurements derived from two dimensional DXA as well as ultrasound (US) measurements of peripheral skeletal sites radius, tibia, and calcaneus significantly correlate with femoral failure load (ranging from $r = 0.37$ to 0.89) and lumbar spine failure load (ranging from $r = 0.37$ to 0.42) (Bouxsein et al., 1999, 1995; Cheng et al., 1998, 1997a, 1997b; Lochmüller et al., 2002; Nicholson et al., 1997). However, generally aBMD measurements at the fracture sites have had stronger correlations with site specific failure load (ranging from $r = 0.75$ to 0.96) as compared to DXA or US measurements at peripheral skeletal sites which did not improve strength predictions (Bouxsein et al., 1999, 1995; Cheng et al., 1998, 1997a, 1997b; Courtney et al., 1995, 1994; Edmondston et al., 1994; Nicholson et al., 1997; Singer et al., 1995).

The primary objective of our study is to use cadaveric specimens to directly measure experimental bone strength at L4 vertebra and proximal femur sites as the reference standard and to determine the correlations with vBMD and FE-determined strength from HR-pQCT at the radius and tibia. Additionally, we perform a direct comparison of DXA-derived aBMD at the L4 vertebra and proximal femur sites to their biomechanical strength to determine how correlations between HR-pQCT measures and failure load compare to the well established relationships between DXA and failure load, and if *in vivo* HR-pQCT scans can contribute to fracture risk assessment in osteoporosis.

2. Methods

2.1. Cadaveric specimens

Bone specimens from ten fresh cadavers were provided by the Gross Anatomy Laboratory at the University of Calgary (8 female, 2 male; aged 76.5 ± 13.1 years). No selection requirements were used, nor was medical history available indicating any previous bone diseases. Pairs of tibia ($n = 20$), radius ($n = 20$), and femurs ($n = 19$) were collected as well as the L4 lumbar vertebra ($n = 9$). One femur was excluded due to a prosthetic hip, and one L4 lumbar spine was not available. All specimens were cleaned of soft tissue, wrapped in saline-soaked gauze, and frozen until testing. All procedures were approved by the University of Calgary Conjoint Health Research Ethics Board.

2.2. Dual energy x-ray absorptiometry

The femurs and lumbar spine specimens were imaged with DXA (Hologic QDR4500, Hologic, Bedford, MA, USA) to measure aBMD (g/cm^2) using standard clinical protocols (Kanis, 1994). To simulate soft tissue attenuation femurs were placed in a saline filled tube for measurement of femoral neck aBMD (Nishiyama et al., 2013a, 2013b). Lumbar spine samples were placed on rice bags to measure L4 aBMD (Burston et al., 1998; Oldroyd et al., 2003).

2.3. High resolution peripheral quantitative computed tomography

Radius and tibia specimens were imaged with HR-pQCT (XtremeCT, Scanco Medical, Brüttisellen, Switzerland) using the standard *in vivo* imaging protocol (60 kVp, 1000 μA, 100 ms integration time) (Boyd, 2008; Cheung et al., 2013; MacDonald et al., 2011). HR-pQCT scans were acquired with a nominal isotropic voxel size of 82 μm. The scan region captured the entire field of view, however, only the region captured in standard *in vivo* scans was analyzed. The analysis region measured 9.02 mm in length, corresponding to 110 axial slices, and started 9.5 mm and 22.5 mm proximal of the reference line location for the radius and tibia, respectively, as per standard protocol. The reference lines were placed at the distal tibial plafond and the inflection point of the distal radial endplate (Boyd, 2008). vBMD was obtained using a standard morphological analysis described in detail elsewhere (MacDonald et al., 2011).

2.4. Finite element modelling

A standard protocol to estimate bone strength from HR-pQCT images was used for FE modelling (MacDonald et al., 2011). The HR-pQCT images were filtered using a Laplace-Hamming filter, and segmented as a basis for homogenous material property models (IPL v5.42, Scanco Medical). Boundary conditions were assigned for uniaxial compression tests with 1% strain (Poisson's ratio = 0.3, Young's modulus = 6829) (MacNeil and Boyd, 2008a). The linear FE models were solved (FAIM 6, Numerics88 Solutions, Calgary, AB, Canada) and failure load was estimated based on the Pistoia criterion (2% critical volume, 7000 critical μ-strain (Pistoia et al., 2002)). The precision of our FE measures are less than 4% root mean squared coefficient of variance based on our previous work (MacNeil and Boyd, 2008b).

2.5. Mechanical testing

The biomechanical strength measures of the femur and vertebra depend on the testing configuration, therefore we attempted to simulate configurations that are representative of loading conditions *in vivo*. For the femoral testing, we chose a sideways fall configuration (Fig. 1) because over 90% of all hip fractures result from a sideways fall in the elderly (Grisso et al., 1991). Mechanical testing of the femur was performed as described by Nishiyama et al. (2013a, 2013b). The femoral head and greater trochanter were embedded in a polymethylmethacrylate (PMMA; Fastray, Bosworth Company, Skokie, IL, USA) cap to aid distribution of loads. Specimens were tested in a material testing system (Instron 8874; Instron Corp; Canton, MA, USA) equipped with a 25 kN load cell (Sensor Data M211-11; Sterling Heights, MI). Specimens were preloaded with 100 N for two seconds before applying a constant displacement of 2 mm/s until the specimens mechanically failed. Failure load was determined from the force-displacement curve as the maximal load measured. This loading rate was lower than a dynamic fall; however, it should be noted that failure load measurements at this rate should not be statistically different from those of loading rates of 100 mm/s as expected in a sideways fall (Courtney et al., 1994) or fall simulations (Gilchrist et al., 2014).

The L4 vertebral bodies were mechanically tested in a uniaxial compression configuration to mimic compression fracture (Fig. 2), which reflects about 25% of all post-menopausal Caucasian women who suffer from vertebral compression fractures in their lifetime, although it is acknowledged that more complex loading conditions may exist (e.g. anterior wedge fractures) (Alexandru and So, 2012; Cummings and Melton, 2002; Genant et al., 2000; Melton et al., 1993). Both ends of the vertebral body were embedded (PMMA, Fastray, Bosworth Company, Skokie, IL, USA) to ensure load distribution. Specimens were mechanically tested using a material testing system (858 Mini Bionix II, MTS, Eden Prairie, MN, USA) equipped with articulating compression platens (MTS 643, MTS) and a 10kN load cell (Force Transducer 661.19, MTS). Specimens were preloaded with 200 N (Hulme et al., 2009), before applying a constant displacement of 0.5 mm/min until the specimens mechanically failed (Wegrzyn et al., 2011). Failure load was determined from the force-displacement curve as the maximal load measured.

2.6. Statistical analysis

Pearson correlations were determined between biomechanical failure load (strength) of the proximal femur or L4 vertebra and all other measurements. All measurements were normally distributed as determined by Shapiro–Wilk tests. These included FE-estimated failure load and vBMD from the distal radius and tibia, as well as DXA-derived aBMD at the proximal femur and L4 vertebra. Multiple correlations were performed to account for there being left and right measurements for tibia, radius, and femur, but not for the centrally located L4 vertebra. As left and right measurements were not independent for a given skeletal site, the mean was calculated and correlations were performed on this summary statistic. This data is referred to as 'pooled' for the remainder of this manuscript. Furthermore, the measurements for the individual sides of the radius, tibia, and femoral aBMD were correlated with femoral failure load in all four possible combinations (left-left, left-right, right-left, right-right) as well as individually correlated with L4 vertebral failure load. For each correlation, we determined p-value p, correlation coefficient r, and number of samples n with the level of significance defined as $p < 0.05$.

Please cite this article in press as: Kroker, A., et al. Distal skeletal tibia assessed by HR-pQCT is highly correlated with femoral and lumbar vertebra failure loads. J. Biomech. (2017), http://dx.doi.org/10.1016/j.jbiomech.2017.05.011

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