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Impact of Charcot neuroarthropathy on metatarsal bone mineral density and geometric strength indices

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ABSTRACT

Charcot neuroarthropathy (CN), an inflammatory condition characterized by rapid and progressive destruction of pedal bones and joints, often leads to deformity and ulceration in individuals with diabetes mellitus (DM) and peripheral neuropathy (PN). Repetitive, unperceived joint trauma may trigger initial CN damage, causing a proinflammatory cascade that can result in osteolysis and contribute to subsequent neuropathic fracture. We aimed to characterize osteolytic changes related to development and progression of CN by measuring bone mineral density (BMD) and geometric strength indices using volumetric quantitative computed tomography. Twenty individuals with DM + PN were compared to twenty age-, sex-, and race-matched individuals with DM + PN and acute CN. We hypothesized that individuals with acute CN would have decreased BMD and decreased total area, cortical area, minimum section modulus, and cortical thickness in the diaphysis of the second and fifth metatarsals. Results showed BMD was lower in both involved and uninvolved feet of CN participants compared to DM + PN participants, with greater reductions in involved CN feet compared to uninvolved CN feet. There was a non-significant increase in total area and cortical area in the CN metatarsals, which helps explain the finding of similar minimum section modulus in DM + PN and CN subjects despite the CN group's significantly lower BMD. Larger cortical area and section modulus are typically considered signs of greater bone strength due to higher resistance to compressive and bending loads, respectively. In CN metatarsals, however, these findings may reflect periosteal woven bone apposition, i.e., a hypertrophic response to injury rather than increased fracture resistance. Future research using these techniques will aid further understanding of the inflammation-mediated bony changes associated with development and progression of CN and other diseases.

Introduction

Diabetes mellitus (DM) and peripheral neuropathy (PN) are the most common precursors of Charcot neuroarthropathy (CN) [1], a progressive, inflammation-mediated destruction of bones and joints leading to fracture, subluxation, and dislocation, which in turn result in progressive foot deformities that increase the risk of plantar ulceration, infection, and ultimately amputation [2–4]. The etiology of CN remains incompletely understood, though previous research suggests that development and progression of CN are related to elevated biomechanical loading [5], joint mal-alignment [6–9] and focal bone loss [6,9,10]. Bone mineral density (BMD) may also affect the clinical manifestation of CN: a clinical presentation of pedal fracture is more common in individuals classified as osteopenic or osteoporotic using dual-energy X-ray absorptiometry (DXA) at the hip, whereas pedal subluxations and dislocations are more common in those with normal or high hip BMD [11]. Acute CN patients have reduced DXA-derived BMD in the lower leg compared to control subjects with neuropathy [12]. Sinacore et al. used quantitative ultrasound (QUS) and found lower estimated calcaneal BMD in CN patients compared to matched non-diabetic controls [6], though Petrova et al. found lower BMD only in CN patients with Type 1 but not Type 2 DM [13].

The metatarsals are the most frequent site of foot fracture [14–16], and a link has been suggested between focal osteopenia and an increased risk of metatarsal fracture [14,17] and "silent" bone stress injuries [18] in individuals with DM and PN. However, neither leg DXA nor calcaneal QUS provides a direct, volumetric assessment of BMD in the pedal bones most prone to fracture: DXA is areal rather than volumetric, QUS provides an indirect measure of BMD, and neither has been used to measure the metatarsals *in vivo*. A semi-automated

Abbreviations: DM, diabetes mellitus; PN, peripheral neuropathy; CN, Charcot neuroarthropathy; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; QUS, quantitative ultrasound; vQCT, volumetric quantitative computed tomography; Tt.Ar, total cross-sectional area; Ct.Ar, cortical cross-sectional area; Ct.Th, average cortical thickness; BR, buckling ratio; I.min, minimum moment of inertia; S.min, minimum section modulus; Met2, second metatarsal; Met5, fifth metatarsal; HU, Hounsfield unit; HA, hydroxyapatite; μCT, micro-computed tomography; HR-pQCT, high-resolution peripheral quantitative computed tomography.

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bone segmentation technique using volumetric quantitative computed tomography (vQCT) to compute bone volumes and BMD for the tarsals and metatarsals has been recently developed [19,20], though the importance of BMD as a predictor of acute or overuse metatarsal fracture remains unclear. In other long bones, geometric strength indices have been more highly correlated to fracture risk than has BMD alone. For example, in the tibia, the strongest predictors of fracture include geometric indices that reflect resistance to compression, such as total (Tt.Ar) and cortical cross-sectional area (Ct.Ar), and resistance to bending loads, such as minimum moment of inertia (I.min) and minimum section modulus (S.min) [21–25]. In the femoral neck, increased fracture risk is associated with indices of cortical buckling, such as decreased cortical thickness (Ct.Th) and increased buckling ratio (BR = periosteal radius/Ct.Th) [26–28]. Reduced Ct.Th and increased BR are thought to be caused by an age-related *homeostatic expansion* of the periosteal surface with a concomitant larger expansion of the endosteal cavity [29–31] which helps to maintain bending strength despite declining bone mineral content [26,32]. The relationship between fracture risk and bone geometry has not been studied in human metatarsals, though in cadavers there are strong correlations between *ex vivo* ultimate loads and BMD [33,34] and indices of bending strength (S.min) and cortical shell integrity (Ct.Th) [35].

The purpose of this study was to characterize bony changes in CN that may lead to increased fracture risk by comparing BMD and bone geometric strength indices in the metatarsals of individuals with DM, PN, and acute CN to a matched group with DM and PN. We hypothesized lower BMD and lower bone strength in compressive (Tt.Ar, Ct.Ar), bending (S.min), and local buckling (Ct.Th) fracture loading modes. The second metatarsal (Met2) and fifth metatarsal (Met5) were chosen as representative medial and lateral column bones, as well as common sites of neuropathic fracture [14,18]. Since Met2 and Met5 may be prone to highly focal inflammation-mediated osteolysis, BMD and geometric strength indices were assessed in discrete locations representing the proximal, central, and distal diaphyseal regions.

Materials and methods

Subjects

Subjects were recruited from the clinical population receiving orthopedic and physical therapy treatment for foot and ankle complications at Barnes-Jewish Hospital and the Washington University School of Medicine in St Louis, Missouri. Twenty individuals with acute onset CN and twenty individuals with DM and PN who did not have CN agreed to participate and provided written informed consent in accordance with the guidelines of the Institutional Review Board and the Human Research Protection Office. Three individuals in the CN group (2 females, 1 male) were excluded from the analysis due to severe joint inflammation in the CN-Involved foot that prevented bone segmentation processing. Demographic data for the 17 remaining CN subjects and the 20 DM + PN subjects are presented in Table 1.

Table 1
Demographic and physical information.

	Diabetes mellitus + peripheral neuropathy (DM + PN)	Charcot neuroarthropathy (CN)	*p* Value
N	20	17	n/a
Sex (F/M)	11/9	9/8	0.90
Ethnicity	13 White 7 African-American	12 White 4 African-American 1 Hispanic	0.44
Age (years)	57.6 ± 10.8	54.9 ± 9.7	0.48
Height (cm)	171.7 ± 8.4	174.2 ± 7.5	0.78
Mass (kg)	94.9 ± 25.7	109.6 ± 26.0	0.09
Body mass index (kg/m^2)	32.0 ± 8.1	36.0 ± 7.7	0.80
Diabetes type (Type 1/Type 2)	2/18	3/14	0.50
HbA1c (%)	7.8 ± 1.4	7.8 ± 1.8	0.99
Diabetes duration (years)	13.9 ± 12.6	17.4 ± 10.8	0.40
Peripheral neuropathy duration (years)	5.2 ± 3.5	7.4 ± 4.8	0.19
Met2 length (mm)	79.4 ± 4.2	78.7 ± 5.7	0.66
Met5 length (mm)	75.4 ± 3.7	73.8 ± 4.5	0.24

Quantitative computed tomography scans and bone segmentation processing

Volumetric QCT scans were taken at the Center for Clinical Imaging and Research at the Washington University School of Medicine using a Siemens SOMATOM Definition CT scanner (Siemens Medical Systems, Malvern, PA, USA) with acquisition parameters of 220 mA·s, 120 kVp, pitch = 1, rotation time 0.33 s, and a 512 × 512 matrix. A B70f reconstruction kernel was used to create vQCT images at 0.6 mm slice interval with in-plane resolution of 0.4–0.55 mm [20,36]. A bone calibration phantom (Image Analysis Inc., Columbia, KY, USA) was included with each scan to allow conversion from x-ray absorptiometry in Hounsfield units (HU) to equivalent calcium hydroxyapatite (HA) concentration in mg/cm^3. The bone segmentation process, which leads to a series of bone object maps (Fig. 1), has been described in detail elsewhere [20,37]. In brief, a density-based filtering algorithm was used to distinguish bone tissue from surrounding soft tissue using ImageJ (NIH Research Services Branch, Bethesda, MD), then bones were segmented from each other at their articulating surfaces using Analyze® software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) and a custom graph-cut software tool [37].

Bone mineral density and geometric strength indices

Following segmentation, bone object maps were overlaid on the raw grayscale voxel data in Analyze® software and interpolated to isotropic voxels (0.5 mm dimensions). The resulting voxel datasets (XYZ position and HU values) for Met2 and Met5 were exported to ImageJ. The BoneJ plug-in [38] was used within ImageJ to compute a density-weighted principal components analysis of the vQCT voxel data (excluding voxels with negative HU values) and transform the voxel data from the vQCT scanner coordinate axes into anatomically-relevant cross-sectional slices perpendicular to each metatarsal's long axis. Realigned voxel data in perpendicular cross-sections were then exported to custom Excel (Microsoft) macros.

In the processing macros, HU values were converted to equivalent BMD (mg/cm^3) using scan-specific HA calibration phantoms [36]. Calculations of bone geometric strength indices were modeled after guidelines for micro-computed tomography (μCT) [39]. For each realigned slice, BMD (mg/cm^3) was computed by first summing the total equivalent bone mineral content (mg), i.e., the product of all positive voxel BMD values and each voxel's volume, then dividing the bone mineral content by the total volume within the periosteal window. S.min (mg mm), which is inversely proportional to bending stress within the bone [40], was calculated by dividing the density-weighted minimum cross-sectional moment of inertia (mg mm^2) by the distance from the density-weighted center of mass to the periosteal edge [35]. Tt.Ar was computed by summing total cross-sectional area within the periosteal envelope, including the medullary cavity, whereas Ct.Ar was computing by summing the cross-sectional area of voxels exceeding a threshold of 300 mg/cm^3 [41]. The spatial resolution of the vQCT scans prevented direct measurement of Ct.Th, and instead the average Ct.Th was computed using Tt.Ar and Ct.Ar with the assumption that the metatarsal diaphysis is roughly a circular annulus. Bone length was computed by multiplying the slice thickness (0.5 mm) by the total number of slices. Proximal, central, and distal diaphyseal regions were defined as 33%, 50%, and 67%, respectively, of the distance from the most proximal slice to the most distal slice of the realigned bones (Fig. 2). For each region, BMD and geometric