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

David J. Gutekunst^a, Kirk E. Smith^b, Paul K. Commean^b, Kathryn L. Bohnert^a, Fred W. Prior^b, and David R. Sinacore^a

Washington University School of Medicine, St. Louis, MO USA

^aApplied Kinesiology Laboratory, Program in Physical Therapy 4444 Forest Park Blvd., Campus Box 8502, St. Louis, MO 63108

^bElectronic Radiology Laboratory, Mallinckrodt Institute of Radiology 4525 Scott Avenue, Campus Box 8131, St. Louis, MO 63110

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.

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Correspondence: David R. Sinacore, sinacored@wustl.edu, Telephone: 00+1 314 362-2407, Fax: 00+1 314 747-0647.

Conflicts of Interest:

For this manuscript Impact of Charcot neuroarthropathy on metatarsal bone mineral density, " and geometric strength indices" all authors state that they have no financial or personal conflicts of interest that could influence the submitted work.

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Keywords

Charcot neuroarthropathy; bone mineral density; computed tomography; diabetes mellitus; peripheral neuropathy

1. 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 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.

2. MATERIALS AND METHODS

2.1 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.

2.2 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 0.33s, and a 512×512 matrix. A B70f reconstruction kernel was used to create vQCT images at 0.6mm slice interval with in-plane resolution of 0.4–0.55mm [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/cm³. The bone segmentation process, which leads to a series of bone object maps (Figure 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].

2.3 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 (0.5mm 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/cm³) 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/cm³) 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. $S_{\min}$ ($\text{mg} \cdot \text{mm}$), which is inversely proportional to bending stress within the bone [40], was calculated by dividing the density-weighted minimum cross-sectional moment of inertia ($\text{mg} \cdot \text{mm}^2$) 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 computed 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 (Figure 2). For each region, BMD and geometric strength indices were averaged over five slices (2.5 mm) to reduce noise.

2.4 Statistical Analyses

Subject sex, ethnicity, and DM type were compared between groups using chi-square tests. Age, height, weight, body mass index, DM duration, and PN duration were compared using the Student's t-test. Additionally, a two-way analysis of variance (ANOVA) (Group * Foot) was used to compare the lengths of Met2 and Met5 to ensure that any differences in $Tt.Ar$, $Ct.Ar$, and $S_{\min}$ were not due to differences in overall bone size. For each dependent variable (BMD, $S_{\min}$, $Tt.Ar$, $Ct.Ar$, and $Ct.Th$), a three-way ANOVA was used to test the effects of Group, Foot, and Region. For CN subjects, foot was coded as Involved or Uninvolved. For DM+PN subjects, neither foot was affected by CN, but for statistical comparisons between the two groups it was necessary to designate one foot per subject as "involved." We arbitrarily chose the right feet of DM+PN subjects as "involved" and then tested the hypothesis that there would be no side-to-side differences in DM+PN subjects. Planned comparisons at each bone region included (a) group comparisons for matched feet (CN-Involved versus DM+PN Right), and (b) side-to-side comparisons within Group (Involved versus Uninvolved for CN subjects and Right versus Left for DM+PN subjects). The significance level was set at $\alpha = 0.05$, with Bonferroni adjustments for multiple post-hoc comparisons. All statistical analyses were completed in SPSS version 20.0 (IBM Corp., Chicago, IL, USA).

3. RESULTS

The two groups did not differ in any demographic or physical characteristics (Table 1). The mean and standard deviation for each combination of group and foot were averaged across the three diaphyseal regions (Table 2). Control DM+PN subjects had no side-to-side differences for BMD or any bone geometric strength measure. When both feet were considered together, BMD showed a significant main effect of group, as CN subjects had 14% lower BMD in Met2 ($p = 0.002$) and 11% lower BMD in Met5 ($p = 0.019$) compared to DM+PN subjects. When CN feet were considered separately, there was significantly 7% lower BMD in the Involved feet compared to the Uninvolved feet for both Met2 and Met5. Both $Tt.Ar$ and $Ct.Ar$ were nominally higher (roughly 10–15%) in CN subjects compared to DM+PN, though neither reached statistical significance for either Met2 or Met5, and there were no side-to-side differences in either areal measure in the CN subjects. $S_{\min}$ was not different between CN and DM+PN, though in Met2 there was a trend for lower $S_{\min}$ in the CN-Involved feet compared to CN-Uninvolved (9% lower, $p = 0.06$) and in Met5 there was a significant 14% reduction in CN-Involved compared to CN-Uninvolved ($p = 0.004$).

When the proximal, central, and distal regions were considered individually, there were no side-to-side differences in DM+PN subjects for BMD or bone geometric strength indices in any region. Thus, DM+PN values are averaged across left and right feet (Figures 3–6). As shown in Figure 3, BMD was significantly lower in CN individuals than DM+PN controls at all regions in both Met2 and Met5. In Met2, the CN-Involved feet had 20% lower BMD than the DM+PN subjects at the proximal region ($p < 0.001$), 16% lower BMD in the central region ($p = 0.001$), and 14% in the distal region ($p = 0.006$). The CN-Involved feet also had 9% lower BMD compared to the CN-Uninvolved feet in the proximal region and central regions (both $p < 0.01$). In Met5, the CN-Involved feet had 16% lower BMD than the DM+PN subjects at the proximal region, 11% lower in the central region, and 20% lower in the distal region. DM+PN controls showed no side-to-side differences, whereas CN individuals had 8% lower BMD in their involved feet compared to uninvolved feet. Regional comparisons showed 5–6% lower BMD in the proximal and central regions of CN-Involved feet compared to Uninvolved ($p > 0.05$), and 14% lower BMD in the distal region ($p = 0.008$).

Compared to DM+PN subjects, the CN subjects had nominally larger ($p > 0.05$) cross-sectional Tt.Ar and Ct.Ar across all regions (Figures 4 and 5). The CN subjects had 11–18% higher Tt.Ar in Met2 and 8–20% higher Tt.Ar in Met5, though only the proximal region of Met2 and the distal region of Met5 showed a trend toward statistical significance, with 20% larger Tt.Ar in the proximal region of Met2 (82 mm² versus 98 mm², $p = 0.055$) and 18% larger Tt.Ar in the distal region of Met5, (62 mm² versus 73 mm², $p = 0.095$).

There were no group differences at any region for S.min in either Met2 or Met5 (Figure 6). The DM+PN subjects showed no side-to-side differences, but the CN-Involved feet had lower values of S.min than CN-Uninvolved at multiple regions: 11% lower for the proximal region of Met2 ($p = 0.029$), 14% lower for the proximal region of Met5 ($p = 0.008$), 13% lower in the central region of Met5 ($p = 0.010$), and 17% lower in the distal region of Met5 ($p = 0.010$). There were no group differences or side-to-side differences for Ct.Th in any region.

4. DISCUSSION

This is the first study to quantify the effects of acute CN on BMD and bone strength-related indices in the metatarsals using vQCT. In both Met2 and Met5, which are common sites of foot fracture [15, 16], we report decreased BMD throughout the diaphysis. The lower BMD in the CN uninvolved feet compared to DM+PN controls suggests a systemic effect of inflammation, with an additional focal effect of inflammation in the CN involved feet. These results reinforce and expand upon previous findings of significant BMD reductions in the calcaneus [6, 13], a predominantly trabecular bone, by showing similar BMD reductions in the diaphyseal region of the metatarsals.

Previous observations of reduced calcaneal BMD were related to inflammation, assessed via pedal skin temperature measurements that showed a 4°C elevation in the involved CN feet [6]. Elevation of pedal temperature provides a clinically observable sign of inflammation and reflects up-regulation of inflammatory pathways in the circulation. Jeffcoate, Game, and Cavanagh [42] first proposed that acute CN is initiated by a minor injury (often undetected) that triggers a cascade of proinflammatory cytokines, including tumor necrosis factor alpha (TNF- α) and interleukin beta (IL- β). Increased levels of proinflammatory cytokines in turn lead to increased expression of NF- κ B and a resulting increase in osteoclastogenesis, which further weakens the bone and leads to neuropathic fracture if loading continues on an insensate foot. This proposed inflammatory mechanism has been corroborated by a recent study comparing peripheral monocytes from acute CN to monocytes from DM+PN controls.

Individuals with acute CN had increased levels of proinflammatory cytokines TNF- α , IL- β , and IL-6, as well as decreased levels of anti-inflammatory cytokines IL-4 and IL-10 [43]. These results support earlier findings that osteoclast activity is elevated in the early stages of CN, with no significant change in osteoblast activity [44].

There is strong epidemiological evidence of increased fracture risk in individuals with both Type 1 [11] and Type 2 DM [45]. In Type 1 DM, the high fracture risk is often attributed to lower BMD [11], though an increased risk of foot and ankle fracture persists even in Type 2 DM individuals with high BMD [45] or when the effects of BMD have been accounted for statistically [46, 47]. Other changes in bone material properties, such as the formation of collagen cross-links, may influence fracture risk in DM [48]. Excepting these glycation-induced changes in bone tissue quality, which were not measured in this study, previous research at other anatomical sites would suggest that the increased fracture risk observed in individuals with DM, PN, and CN would be associated with decreased geometric strength indices such as S.min, Tt.Ar, Ct.Ar, and Ct.Th, which have been predictive of fracture risk in the tibia [21, 22, 49], femur [27, 49, 50], and metatarsals [34, 35]. Most relevant to the current study is a recent cadaver validation of the vQCT-based techniques to quantify BMD and geometric strength indices [35], in which S.min and Ct.Th were the strongest predictors of *ex vivo* bone strength, together accounting for 85–89% of the variance in ultimate force measured during three-point bending tests.

Results from the present analysis are mixed: we report reduced BMD in both Met2 and Met5 at all regions within involved and uninvolved CN feet, but with maintenance of Ct.Th and non-significant elevation of Tt.Ar, Ct.Ar, and S.min. Based on previous research, these geometric results would suggest that CN metatarsal strength may be maintained, which is unexpected given the known fracture risk in CN metatarsals. One explanation for the reduction in BMD with maintained geometric strength indices is that the CN bones are responding functionally by increasing resistance to bending and buckling loads.

This investigation has limitations. First, the relatively small sample size may contribute to the non-significant findings for geometric strength properties by increasing the risk of a Type II error. Second, our methods are presently limited to research applications and not sufficiently rapid for routine clinical use as a diagnostic tool. Third, vQCT scans expose subjects to ionizing radiation, though foot and ankle scans do not expose sensitive organs directly to radiation.

Additionally, current vQCT technology does not permit precise quantification of parameters such as cortical porosity or woven bone formation. Thus the observed non-significant elevation in Ct.Ar may reflect the metatarsals' response to injury rather than a true cortical expansion that would impart greater mechanical strength in compression and bending. The spatial resolution used in this analysis (0.5 mm isotropic voxels), while near the current limits of clinical vQCT capabilities, leads to spatial averaging of bone and non-bone material. As a result, it is more difficult to set a precise threshold to distinguish bone from marrow, or trabecular bone from cortical bone. Choosing a threshold that is too low can lead to inclusion of voxels that are not predominantly cortical bone and an overestimation of Ct.Ar and Ct.Th, but choosing a threshold that is too high can lead to erroneous discontinuities in the thinning cortical shell. Others have encountered similar issues with spatial averaging and have chosen the same threshold (300 mg/cm³) to define bone and non-bone material [41]. A recent study using high-resolution peripheral QCT (HR-pQCT) in the radius and tibia of Type 2 DM patients reported higher values for geometric indices of bone strength, as we have shown here, but inefficient redistribution of bone mass that could result in impaired bending strength [51]. Future imaging studies of CN foot bones with improved spatial resolution, such as *in vivo* HR-pQCT or cadaver studies using μ CT, will limit the

effects of spatial averaging, permit a more precise threshold to be applied, and provide a clearer understanding of what is occurring at the structural level of CN bone.

5. CONCLUSIONS

We have applied novel techniques to assess region-specific BMD and bone geometric strength indices in the neuropathic foot using clinical vQCT. In individuals with acute CN, we report reduced BMD at all regions in both the involved and uninvolved CN feet, with significantly greater bone reductions in the involved feet compared to uninvolved. There were non-significant elevations in CN subjects for indices of bone strength in compressive loading (Ct.Ar), bending (S.min), and cortical buckling (Ct.Th), though these findings may reflect an incomplete hypertrophic response to injury rather than a true improvement in fracture resistance. Future research using the methodologies presented here will assess changes in BMD and geometric indices as CN progresses from the acute stage, as well as identify bone properties that may predict which individuals with DM and PN will go on to develop CN. Finally, future imaging studies may help elucidate the pathophysiological links between inflammation, altered bone morphology, and fracture risk in Charcot neuroarthropathy.

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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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Highlights

- Quantitative computed tomography image processing techniques were used to assess foot bone strength noninvasively in acute Charcot neuroarthropathy.
- BMD was lower in Charcot patients versus diabetic, neuropathic controls, but indices of compressive and bending strength were maintained.
- Geometric results may reflect an inflammation-mediated response to bone injury rather than true maintenance of bone strength.
- Clinical quantitative computed tomography precludes clear discernment between functional bone adaptation and injury response, such as woven bone apposition.
- Improved spatial resolution will clarify the effects of Charcot neuroarthropathy on lower extremity bone strength and fracture risk.

Figure 1. Bone segmentation processing. Raw vQCT image and filtered, segmented, filled bone object maps for tarsals and metatarsals for (A) CN-Involved foot and (B) CN-Uninvolved foot.

Figure 2.
Exemplar sample of a segmented second metatarsal showing diaphyseal regions (top) and associated bone mineral density profile along the bone's longitudinal axis (bottom)

Figure 3.

Bone mineral density (mg/cm^3) in the proximal, central, and distal diaphyseal regions of (A) Metatarsal 2, and (B) Metatarsal 5. * $p < 0.01$ compared to DM+PN; †† $p < 0.01$ compared to CN-Uninvolved.

Figure 4. Total cross-sectional area, Tt.Ar (mm²) in the proximal, central, and distal diaphyseal regions of (A) Metatarsal 2, and (B) Metatarsal 5.

Figure 5.
Cortical cross-sectional area, Ct.Ar (mm²) in the proximal, central, and distal diaphyseal regions of (A) Metatarsal 2, and (B) Metatarsal 5.

Figure 6.

Minimum section modulus, S_{min} (mg*mm) in the proximal, central, and distal diaphyseal regions of (A) Metatarsal 2, and (B) Metatarsal 5. † $p < 0.05$ compared to CN-Uninvolved; †† $p < 0.01$ compared to CN-Uninvolved.

Table 1

Demographic and physical information.

	Diabetes Mellitus + Peripheral Neuropathy (DM +PN)	Charcot Neuroarthropathy (CN)	P value
<i>N</i>	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 (Type1/Type2)	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

Table 2
Bone mineral density and bone geometric strength indices, averaged across diaphyseal regions.

	Diabetes Mellitus Peripheral Neuropathy (DM+PN)		Charcot Neuroarthropathy (CN)				Main effect: DM+PN vs CN
	Left (L)	Right (R)	L vs R	Uninvolved (U)	Involved (I)	U vs I	
<i>BMD (mg/cm³)</i>							
Met2	1117 ± 141	1105 ± 134	$p = 0.60$	997 ± 157	923 ± 155	$p = 0.005$	$p = 0.002$
Met5	946 ± 147	962 ± 137	$p = 0.54$	877 ± 131	814 ± 162	$p = 0.026$	$p = 0.019$
<i>Tt.Ar (mm²)</i>							
Met2	62.1 ± 10.2	64.1 ± 12.7	$p = 0.20$	73.7 ± 19.8	72.8 ± 25.0	$p = 0.79$	$p = 0.07$
Met5	86.2 ± 19.2	86.5 ± 18.0	$p = 0.83$	95.1 ± 26.7	95.8 ± 24.7	$p = 0.80$	$p = 0.21$
<i>Ct.Ar (mm²)</i>							
Met2	43.6 ± 7.1	45.0 ± 9.4	$p = 0.52$	51.6 ± 13.1	51.1 ± 21.3	$p = 0.83$	$p = 0.10$
Met5	53.2 ± 10.5	54.6 ± 10.7	$p = 0.36$	61.8 ± 17.0	59.4 ± 15.4	$p = 0.17$	$p = 0.13$
<i>S.min (mg*mm)</i>							
Met2	28.5 ± 5.8	29.6 ± 7.7	$p = 0.36$	31.4 ± 10.7	28.8 ± 11.6	$p = 0.061$	$p = 0.72$
Met5	31.1 ± 11.6	32.7 ± 10.7	$p = 0.31$	37.3 ± 16.7	32.0 ± 14.6	$p = 0.004$	$p = 0.52$
<i>Ct.Th (mm)</i>							
Met2	2.05 ± 0.28	2.06 ± 0.33	$p = 0.80$	2.17 ± 0.37	2.15 ± 0.62	$p = 0.86$	$p = 0.51$
Met5	2.02 ± 0.27	2.08 ± 0.28	$p = 0.29$	2.23 ± 0.40	2.14 ± 0.39	$p = 0.22$	$p = 0.19$