Inflammatory Osteolysis in Diabetic Neuropathic (Charcot) Arthropathies of the Foot

David R Sinacore, Mary K Hastings, Kathryn L Bohnert, Faye A Fielder, Dennis T Villareal, Vilray P Blair III, Jeffrey E Johnson

Objective. Osteolysis and low bone mineral density (BMD) are underappreciated consequences of several chronic diseases that may elevate the risk for fracture. The purpose of this study was to assess tarsal BMD associated with acute inflammation (ie, inflammatory osteolysis) in individuals with chronic diabetes mellitus (DM), peripheral neuropathy (PN), and recent-onset neuropathic (Charcot) arthropathy (NCA) of the foot.

Research Design and Methods. This was a case-control study of 32 people (11 men, 21 women) with DM, PN, and NCA of the foot or ankle. The subjects with DM, PN, and NCA were compared with 64 age-, sex-, and race-matched control subjects (24 men, 40 women) without DM, PN or NCA. Within the first 3 weeks of cast immobilization, BMD was estimated in both calcanei using quantitative ultrasonometry. Acute inflammation was confirmed by comparing skin temperature differences between the feet of the subjects with DM, PN, and NCA and the feet of the control subjects.

Results. Skin temperature differences averaged 6.7°F (SD=4.0°F) (involved foot minus noninvolved foot) in the feet of the subjects with DM, PN, and NCA compared with 0.0°F (SD=1.3°F) in the feet of the control subjects. Calcaneal BMD averaged 384 mg/cm² (SD=110) in the involved feet and 467 mg/cm² (SD=123) in the noninvolved feet of the subjects with DM, PN, and NCA and 545 mg/cm² (SD=121) in combined right and left feet of the control subjects.

Conclusions. Inflammation in individuals with DM, PN, and NCA may contribute to or exacerbate a rapid loss of BMD. Inflammatory osteolysis may be a prominent factor responsible for both the spontaneous onset of neuropathic fracture and the insidious and progressive foot deformity that is the hallmark of the chronic Charcot foot.

DR Sinacore, PT, PhD, FAPTA, is Associate Professor, Department of Medicine and Program in Physical Therapy, and Director, Applied Kinesiology Laboratory, Campus Box 8502 Washington University School of Medicine, 4444 Forest Park Blvd, St Louis, MO 63108 (USA). Address all correspondence to Dr. Sinacore at: sinacored@wustl.edu.

MK Hastings, PT, DPT, ATC, is Assistant Professor, Program in Physical Therapy and Department of Orthopaedic Surgery, Washington University School of Medicine.

KL Bohnert, MS, CDT, is Research Coordinator and Certified Densitometry Technologist, Applied Kinesiology Laboratory, Program in Physical Therapy, Washington University School of Medicine.

FA Fielder, RN, APRN, BC, is board-certified Adult Practice Nurse, Foot and Ankle Service, Department of Orthopaedic Surgery, Washington University School of Medicine.

DT Villareal, MD, is Associate Professor, Department of Medicine, Washington University School of Medicine.

VP Blair III, MD, is Private Practice Associate, West County Bone and Joint Associates, St Louis, Missouri.

JE Johnson, MD, is Associate Professor, Department of Orthopaedic Surgery, Chief, Foot and Ankle Service, Washington University School of Medicine.

Post a Rapid Response or find The Bottom Line: *www.ptjournal.org*

Osteolysis (bone loss) is an underappreciated consequence of a number of chronic diseases that may elevate the risk for fracture. In some individuals with diabetes mellitus (DM) and peripheral neuropathy (PN), repetitive trauma may combine with exaggerated bone loss to manifest in serious pedal complications such as acute neuropathic (Charcot) arthropathy (NCA) that can leave the foot deformed and unstable for weight bearing.[1,2]

Neuropathic (Charcot) arthropathy is an insidious, noninfective, and progressive destruction of bones and joints, resulting in pathological fractures, dislocations, or subluxations. There have been 2 dozen or more chronic diseases in which neuropathic fractures and joint changes have been described.[1] Since a 1936 report by Jordan,[3] DM has been recognized as the primary disease in which NCA most often occurs. Despite the prevalent conditions in which NCA can develop, the etiogenesis of acute NCA in the foot remains poorly understood. The contemporary view is that acute NCA is an amalgam of PN, unperceived and repetitive trauma, acute inflammation, and an underlying propensity for bone weakness.[1]

The purpose of this matched case-control study was to assess the extent of osteolysis that may accompany acute inflammation in individuals with DM, PN, and NCA of the foot.

Research Design and Methods

We group-matched 64 control subjects (24 men, 40 women) for age, sex, and race with 32 case subjects (11 men, 21 women) with DM, PN, and an acute, unilateral inflammation due to recent-onset NCA. The control subjects had no history of trauma to either foot. All case subjects had been previously diagnosed with DM, had PN confirmed at their initial physical therapy visit, and had an arthropathy for which they were seeking treatment and either were being followed in our weekly diabetic foot clinic or were referred to our physical therapy service for total contact cast immobilization over a 36-month period.[4] Inclusion criteria for the case subjects included a radiograph-confirmed overt fracture or joint change (subluxation or dislocation) consistent with NCA and no evidence of local infection, osteomyelitis, or advancing cellulitis. Three of the 32 subjects had accompanying plantar ulceration. The plantar ulcer was remote from the primary fracture or joint dysfunction in 2 subjects and was directly beneath the fracture location in 1 subject.

All case subjects' Charcot arthropathy was temporally staged as Eichenholtz acute or subacute stage[5] by history, clinical examination, and standard radiographs. The average duration of time prior to seeking therapy for their arthropathy was determined by interview and subject self-report. On average, most subjects delayed seeking treatment for 4 to 7 weeks prior to their initial visit for cast immobilization. Forty-three percent of the subjects reported that their current arthropathy was their first onset, whereas 57% of the subjects reported at least one prior onset in the same foot location or in a different location within the same foot. No subject with DM, PN, and NCA had been diagnosed with renal or hepatic osteodystrophy, none stated they were current smokers, and none had taken oral steroids within the past 2 years. Female subjects were not receiving hormone replacement therapy or oral contraceptive therapy.

Neuropathy, Inflammation, and Pedal Bone Mineral Density

The presence or absence of PN was not a strict inclusion or exclusion criterion for the case subjects at the outset of our study. Similar to the diagnosis of DM, PN was a common impairment that characterized all of our case subjects. The presence or absence of PN was assessed in each subject at the initial physical therapy visit or visit to our diabetic foot clinic. We assessed light touch (pressure) at 7 locations on the plantar surface of each foot (dorsal midfoot, first, third, and fifth metatarsal heads; and medial and lateral midfoot and central hindfoot) was assessed using a single-thickness (5.07/10-g) Semmes-Weinstein monofilament.[6] Subjects who were unable to accurately sense the 5.07 monofilament at any one of 7 locations were graded as absent protective sensation and were considered to have PN.

To confirm the presence of inflammation, we assessed the skin temperature at the same 7 locations on each foot using an Exergen infrared dermal thermometer (model DT1001*).[7] The interval of time from onset of symptoms to skin temperature assessments in the subjects with DM, PN, and NCA varied, although it was estimated from the subjects' verbal reports to be 4 to 7 weeks prior to the initial physical therapy visit and the start of therapy (casting) in the majority of subjects.

All subjects were asked to remove their socks and footwear and to rest comfortably on an examination table for at least 15 minutes prior to assessing skin temperature. We performed 3 trials of skin temperature assessment at each of 7 locations in the foot in a standardized, ordered sequence.[7] The 3 measurements taken at each location were averaged to obtain a single average skin temperature for each foot location. The average skin temperature difference at each site in the noninvolved foot (without NCA) was subtracted from

---

* Exergen Corp, 400 Pleasant St, Watertown, MA 02472.

the corresponding skin temperature in the involved foot (with NCA) of the subjects with DM, PN, and NCA and expressed as an average skin temperature difference. In the control subjects, the same procedure was used, subtracting the right foot temperature from the corresponding locations on the left foot. All skin temperatures were recorded in degrees Fahrenheit. Core body temperature was assessed at the mouth using Tempa-Dot,[†] and room temperature was recorded immediately prior to the first skin temperature assessment of each subject using the Exergen thermometer.

During the same visit as the skin temperature assessment, we assessed several measures of bone quality, including estimating bone mineral density (BMD) of both feet in each subject using quantitative ultrasonometry (QUS) (Sahara Clinical Bone Sonometer[‡]). Ultrasound measures included the speed of sound (SOS, in meters per second), broadband ultrasound attenuation (BUA, in decibels per megahertz), quantitative ultrasound index (QUI, or the slope of the BUA:SOS measures), estimated bone density (BMD, in milligrams per square centimeter), and T-score (the number of standard deviation units above or below the norm for a young, adult female population).[8] Bone quality indicators, including SOS, BUA, and QUI, are believed to represent several bony microarchitectural properties such as trabecular geometry, thickness, and stiffness parameters that, independently of BMD, correlate with dual-energy x-ray absorptiometry (DXA)–derived BMD and relative fracture risk.[8]

The same research assistant (KLB) performed all skin temperature and QUS assessments. Two trials of each subject's calcaneus were performed using the standard sequence of the right foot, left foot, right foot again, then left foot again. Measurements obtained during the 2 trials of each foot were averaged and expressed as a single value for each calcaneus. The precision of BMD estimates in the heel has been reported to be excellent using ultrasonometry.[9] Our sonometer was calibrated according to the manufacturer's instructions before each subject visit. We have previously assessed the reliability and precision of all of the bone quality measures.[10] Coefficients of variation (CVs) from 8 measures over a 4-week period on a cadaver foot-phantom ranged from 0.2% for SOS, 1.9% for QUI, 3.5% for BUA, and 2.2% for estimated BMD.[10] Intraclass correlation coefficients (3,1) calculated from test-retest measurements at a 1-week interval in 20 subjects who were healthy ranged from .86 for BUA, .96 for SOS, .97 for QUI, and .97 for estimated BMD.[10]

All subjects read and signed an informed consent statement prior to their participation. Subjects were not remunerated for their participation.

Data Analysis
The cohort characteristics of age, height, body mass, BMI, and shoe size were assessed using a *t* test for independent samples. The Kruskal-Wallis nonparametric test was used to assess equivalency of sex, race, and frequency of neuropathy in each cohort. The skin temperature differences at the 7 locations in the feet of in the subjects with DM, PN, and NCA were averaged and compared with those of the control subjects using *t* tests for independent samples. The BMD, SOS, BUA, and QUI measurements and T-scores of the calcaneus in the involved foot were compared with those of the nonin-

volved foot in the subjects with DM, PN, and NCA and with the average of both heels in the control subjects using a one-way analysis of variance.

Results
The physical characteristics of each cohort are shown in Table 1. Group matching procedures for age, sex, race, and shoe size were successful, as baseline physical characteristics were not significantly different between the cohorts. Body mass, BMI, and the presence of PN were greater and more prevalent in the subjects with DM, PN, and NCA than in the control subjects.

Room temperature remained relatively constant over the data collection phase of this study. The average room temperature was 72.4°F (SD=4.3°F) during all assessments. Core body temperature averaged 98.1°F (SD=0.6°F) for all subjects with DM, PN, and NCA and 97.9°F (SD=0.9°F) for the control subjects (*P*=.200, Tab. 1).

Foot skin temperature differences were significantly greater in the subjects with DM, PN, and NCA compared with the control subjects. The average skin temperature difference was 6.7°F (SD=4.0°F) higher in the involved foot of the subjects with DM, PN, and NCA compared with an average of 0.0°F (SD=1.3°F) for the control subjects (*P*<.00, Tab. 2). There was no significant difference in absolute skin temperatures between the control subjects' feet and the noninvolved foot of the subjects with DM, PN, and NCA at any of the plantar sites except the dorsal surface of the midfoot, where absolute skin temperatures averaged 85.9°F (SD=3.4°F) in the feet of the control subjects and 82.7°F (SD=4.8°F) in the noninvolved foot of the subjects with DM, PN, and NCA (*P*<.00, data not shown). These lower average skin temperatures in the noninvolved foot of the subjects with DM,

---

Table 1.
Physical Characteristics of Subjects With Diabetes Mellitus (DM), Peripheral Neuropathy (PN), and Recent-Onset Neuropathic (Charcot) Neuropathy (NCA) and Control Subjects[a]

Characteristic	Subjects With DM, PN, and NCA (n=32)	Control Subjects (n=64)	P
Age (y)	55±11	51±16	.252
Height (cm)	172.2±13.4	170.7±10.0	.526
Body mass (kg)	100.5±23.3	73.9±14.5	.000
Body mass index (kg/m²)	33.8±6.3	25.3±4.0	.000
Sex (male/female)	11/21	24/40	.765
Race (white/black/Asian)	28/4/0	58/4/2	.681
Neuropathy (able to sense 10-g monofilament)	0	64	.000
European shoe size (cm)	42±4	41±3	.434
Body temperature (°F)	98.1±0.6	97.9±0.9	.200
Diabetes type (1/2)	9/23	NA	NA
Diabetes duration (y)	18±13	NA	NA
Involved foot (left/right/both)	25/6/1	NA	NA
Arthropathy location	1 hindfoot, 14 midfoot, 8 forefoot, 5 ankle, 4 mixed	NA	NA
Duration of inflammation present prior to seeking treatment (wk)	4±3	NA	NA

[a] Data are means (±SD). NA=not applicable.

PN, and NCA compared with the control subjects' feet may reflect early, mild vascular involvement in people with DM, PN, and NCA.

The means and standard deviations for the ultrasound measures are summarized in Table 2. All bone quality measurements were significantly lower in the feet of the subjects with DM, PN, and NCA than in the control subjects' feet (P<.00 for all variables, Tab. 2). The SOS averaged 1.2% lower, the BUA averaged 20.6%

Table 2.
Ultrasonic Bone Measures and Skin Temperature Differences in Subjects With Diabetes Mellitus (DM), Peripheral Neuropathy (PN), and Recent-Onset Neuropathic (Charcot) Neuropathy (NCA) and Control Subjects[a]

Variable	Subjects With DM, PN, and NCA (n=32)	Control Subjects (n=64)	P
Estimated BMD (mg/cm²)	425±123	545±121	.000
SOS (m/s)	1,526±31	1,544±135	.000
BUA (dB/MHz)	59.9±21.8	75.4±16.6	.000
QUI	79.7±19.6	98.2±19.4	.000
T-score (SD units)	−1.38±1.10	−0.33±1.1	.000
Foot skin temperature difference (°F)	6.7±4.0	0.0±1.3	.000

[a] Data are means (±SD). All values for subjects with DM, PN, and NCA are for involved foot with NCA and noninvolved foot without NCA combined; control subjects' values represent right and left feet combined. SOS=speed of sound; BUA=broadband ultrasound attenuation; QUI=quantitative ultrasound index) or "stiffness," a unitless linear combination representing the slope of the BUA:SOS measures; T-score is the number of standard deviation units from the average value obtained from a reference sample of 20- to 29-year-old white female subjects.

lower, and the QUI averaged 18.8% lower in the feet of the DM, PN, and NCA subjects than in the control subjects' feet.

In the subjects with DM, PN, and NCA, the mean BMD was 384 mg/cm² (SD=110) in the calcaneus of the involved foot and 467 mg/cm² (SD=123) in the calcaneus of the noninvolved foot (P<.000). The calcaneal BMD of the right and left feet (combined) of the control subjects averaged 545 mg/cm² (SD=121) (F=19.1; df=2,125; P<.005; Fig. 1). The calcaneal BMD of the involved foot was 18% lower than that of the noninvolved foot (absolute decrease of 83 mg/cm²) in the subjects with DM, PN, and NCA and 29% lower than the calcaneal BMD of the control subjects' feet. The calcaneal BMD of the noninvolved foot in the subjects with DM, PN, and NCA was 14% lower than the calcaneal BMD of the control subjects' feet (P<.002).

The average T-scores for the involved foot (average=−1.81, SD=0.9) and the noninvolved foot (average=−0.95, SD=1.1) in the subjects with DM, PN, and NCA and for both feet (combined) of the control subjects (average=−0.33, SD=1.09) are illustrated in Figure 2. The involved foot had a significantly lower T-score compared with the noninvolved foot and the control subjects' feet (P<.000). The noninvolved foot had a lower T-score than that of the control subjects' feet (P<.006).

According to World Health Organization criteria for classification of T-scores,[8] in the subjects with DM, PN, and NCA, 24% of the women and 18% of the men were classified as osteoporotic, 62% of the women and 64% of the men were classified as osteopenic, and 14% of the women and 18% of the men were classified as having normal pedal BMD. In the control subjects, 1 woman (1.5%) and no men (0%) was classified as

osteoporotic, 11% of the women and 8% of the men were classified as osteopenic, and 80% of the women and 79% of the men were classified as having normal pedal BMD.

Discussion

Subjects with DM, PN, and NCA had reduced pedal bone quality and estimated density in both feet (combined) and in the involved foot and noninvolved foot (when analyzed separately) compared with the control subjects' feet. In addition to estimated BMD, bone quality indicators (eg, SOS, BUA, and QUI) representing bony microarchitectural properties of trabecular bone were lower in the calcaneal bones of the subjects with DM, PN, and NCA compared with the control subjects' feet.

Interestingly, calcaneal BMD and T-scores were lower in the noninvolved foot of the subjects with DM, PN, and NCA compared with control subjects' feet. Despite lower BMD in the noninvolved foot, the absolute skin temperatures were similar to (or lower than) control subjects' absolute skin temperatures, suggesting that the presence of DM and PN may reduce tarsal BMD preceding and independent of elevated foot temperatures. However, we cannot rule out the possibility that a local inflammatory increase in an involved foot of the subjects with DM, PN, and NCA may have contributed to a circulating systemic stimulus for bone loss in the contralateral noninvolved foot.

Some investigators have shown a direct, positive association between elevated body mass and higher bone mass at all skeletal sites,[11] suggesting that an elevated body mass may be osteoprotective against low-trauma, fragility fractures. Our subjects with DM, PN, and NCA were obese (some markedly), based on the World Health Organization classification.[12]
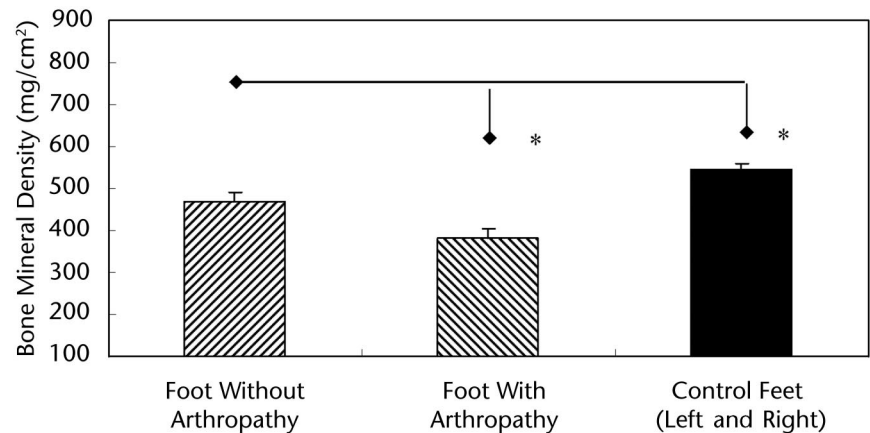

Figure 1.
Quantitative ultrasound-derived bone mineral density in the calcaneus of the foot without arthropathy and in the calcaneus of the foot with arthropathy of the subjects with diabetes mellitus, peripheral neuropathy, and recent-onset neuropathic (Charcot) neuropathy and in the calcaneus of the left foot and the calcaneus of the right foot (combined) of the control subjects. Data are mean (and SD). Asterisk indicates different than foot without arthropathy; $P < .000$ for all comparisons.

Despite a significantly greater body mass and being classified as obese, our subjects with DM, PN, and NCA had a significantly lower pedal bone density, with T-scores indicating a greater prevalence of osteopenia or osteoporosis even prior to cast immobilization compared with our control group. The mechanism mediating the loss of osteoprotection against low-trauma, fragility fractures is yet unknown. An elevated level of circulating inflammatory cytokines such as tumor-necrosis factor-alpha, interleukin-1 or interleukin-6[13] combined with neuropathy-induced un-
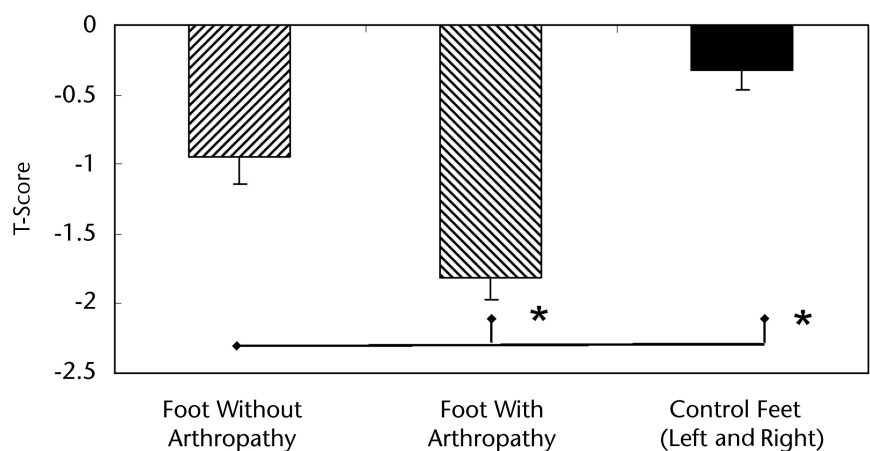

Figure 2.
T-scores in the calcaneus of the foot without arthropathy and in the calcaneus of the foot with arthropathy of the subjects with diabetes mellitus, peripheral neuropathy, and recent-onset neuropathic (Charcot) neuropathy and in the calcaneus of the left foot and the calcaneus of the right foot (combined) of the control subjects. T-score represents the number of standard deviations below the mean T-score of a reference sample of 20- to 29-year-old white female subjects. Data are mean ($\pm$SD). Asterisk indicates different than foot without arthropathy; $P < .000$ for all comparisons.

coupling of bone osteoblastic and osteoclastic rates may likely combine to favor a net pedal bone loss.[14]

The presence of acute inflammation accompanying onset of NCA may directly or indirectly mediate the loss in pedal bones. Excessive bone loss due to joint inflammation has previously been reported in inflammatory conditions such as rheumatoid arthritis,[15,16] although often overlooked as a complication to chronic DM, PN, and diabetic foot disease. Inflammation-mediated bone loss in rheumatoid arthritis can occur independent of chronic steroid use.[17,18] Inflammation-induced bone loss has previously been demonstrated to be quite rapid as well as profound. Armour et al[19] have shown a dramatic 14% reduction in trabecular and cortical BMD at the tibial metaphysis of mice only 21 days after the induction of systemic inflammation. We observed a comparable 18% reduction in calcaneal BMD in the foot with acute inflammation compared with the noninvolved foot in our subjects with DM, PN, and NCA.

Bone loss in the feet of our subjects with DM, PN, and NCA appeared to be cumulative and most likely the result of several synergistic factors. Individuals with chronic DM and peripheral somatic and autonomic neuropathy are known to lose bone at rates faster than age-related declines.[20] Menopause-related bone loss exceeds age-related bone loss during the first 5 years after menopause, as women typically can lose as much as 15% of their bone mass in the first decade after menopause.[21,22] In our study, 21 of the 32 subjects with DM, PN, and NCA were women. Upon routine questioning at the time of QUS assessments, these subjects indicated they either had undergone premature menopause or were irregularly menstruating for several years prior to onset of their arthropathy. When an-

alyzing our cohort with DM, PN, and NCA for sex differences, we could not detect greater inflammation (ie, a greater difference in foot skin temperatures) or greater osteolysis in women compared with men in our small sample of subjects. In our subjects with DM, PN, and NCA, women had an average foot skin temperature difference of 6.1°F (SD=4.4°F), and men had an average foot skin temperature difference of 7.7°F (SD=3.8°F) (P=.156, nonsignificant). Women in this group had an average calcaneal BMD of 370 mg/cm² (SD=94) in the involved foot compared with men's average calcaneal BMD of 409 mg/cm² (SD=136), an average of 9.5% lower (P=.204, nonsignficant). Early menopause in the women in this group may have played an indirect, permissive role in pedal osteolysis.

Another factor that could have affected our results was physical inactivity. Although we did not assess this factor directly, our subjects with DM, PN, and NCA may have experienced a prolonged period of physical inactivity prior to onset of their NCA that resulted in disuse-induced osteopenia, thereby contributing to the cumulative bone loss that we observed. Maluf and Mueller[23] reported that subjects with DM and PN with or without a recurrent plantar ulcer walked an average of 46% and 22% fewer daily steps, respectively, compared with control subjects without DM or PN. For additional discussion of physical inactivity in this population, see the related articles by LeMaster et al[24] and Deshpande et al[25] in this issue. Synergistic factors such as early menopause, disease-related (chronic DM and PN) decline, physical inactivity, and inflammation-mediated bone loss most likely combined for the significant reductions in pedal BMD that we observed. Despite our matched case-control design, we are unable to attribute the profound loss of pedal bone en-

tirely to the local acute inflammatory responses in NCA because other factors may have synergistically contributed.

Pedal Inflammation as a Biomarker of Osteolysis and NCA Outcomes

The duration and severity of pedal inflammation are likely 2 key factors contributing to the rapid osteolysis in people with acute arthropathy of the foot.[7,26] As is typical in patients with neuropathy, many of our subjects had reported an onset of minor trauma several weeks prior to seeking and initiating their medical treatment.[4] It is quite common that subjects with DM and loss of protective sensation may experience several weeks of exaggerated inflammation of their foot, resulting in accelerated bone resorption. As we assessed only skin temperature on their initial physical therapy visit prior to initiation of treatment with total contact cast immobilization, it is likely that the inflammatory response may have been further elevated and prolonged.

The persistence and magnitude of pedal inflammation have been used as clinical biomarkers of healing in the acute and subacute stages of Charcot arthropathy in previous studies.[7,26] Armstrong and Lavery[26] recommended a skin temperature difference at involved sites or the entire foot of no more than 1°C (1.8°F) as the maximum difference for 2 consecutive weeks in order to transition patients with neuropathy from cast immobilization to removable cast boots and then an additional 4 weeks of skin temperature equilibrium to transition to therapeutic footwear in order to prevent NCA recurrence. Although these guidelines may serve the clinician regarding local inflammation, more study is needed to determine the effect of acute inflammation and utility of skin temperature elevations on the magnitude and timing of pedal osteolysis

as well as the outcomes after acute NCA.

Whether pedal inflammation, as indicated by skin temperature monitoring, reflects bone and joint healing or predicts the amount of bone lost in all the tarsals and metatarsals has not been adequately studied. McCrory et al[27] studied 6 subjects with acute Charcot midfoot fractures and concluded that skin temperatures are much too variable and not clinically useful because they do not correlate with standard, weight-bearing radiographic evidence of fracture healing or progression. Standard radiographs are notoriously poor indicators of bone density as well as acute bone loss, and bony changes become evident on radiographs only after well-established disease.[28]

The results of our study suggest that pedal inflammation, as indicated by local skin temperature elevations, may be associated with QUS-derived calcaneal bone loss; however, the extent to which inflammation reflects bone loss in all of the tarsals and metatarsals remains the focus of future study.[29,30] We speculate that pedal osteolysis may be a key biomarker that can predict outcomes after NCA, particularly the onset of fixed foot deformities.[30]

Sequelae of Osteolysis and Clinical Implications

Inflammation-mediated pedal osteolysis may have residual sequelae long after resolution of the acute and subacute stages of arthropathy healing. Bony destruction and collapse of the longitudinal and transverse arches of the foot often result in severe foot deformities that can leave the foot unstable for normal weight bearing, require custom-fabricated footwear and bracing, and lead to plantar ulceration (Fig. 3).[1,2] (Also see the related article about neuropathic ulcers by Mueller et al[31] in this issue.) In turn, chronic nonhealing ulceration and
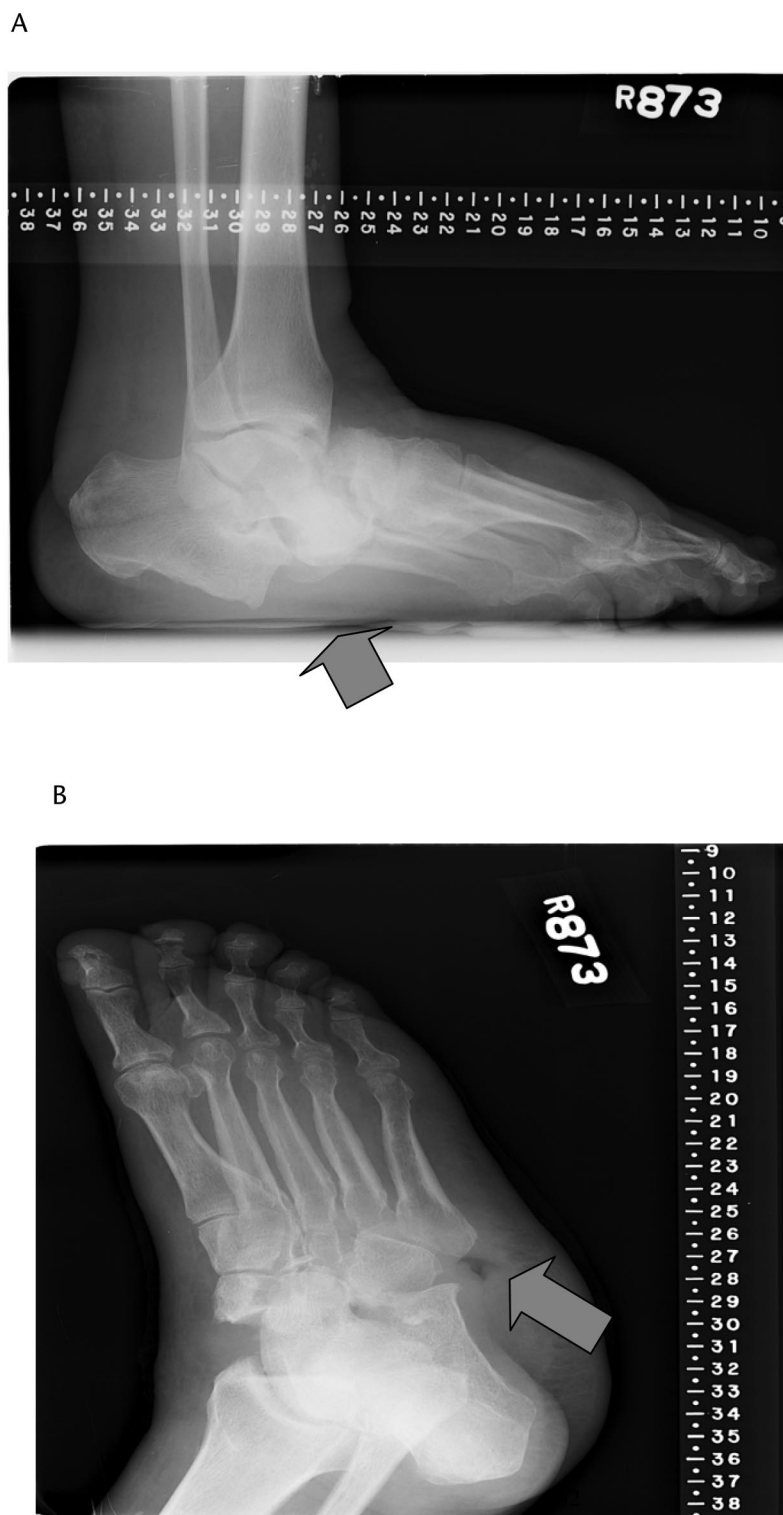
A

B

Figure 3.
Weight-bearing radiographs (lateral view in radiograph A and oblique view in radiograph B) of a 57-year-old man with type 2 diabetes mellitus, peripheral neuropathy, and an acute neuropathic (Charcot) arthropathy of the right midfoot with accompanying midfoot ulceration. Arrow in radiograph A indicates severely dislocated head of the talus and reduced angle of the calcaneus. Arrow in radiograph B indicates plantar ulceration beneath the calcaneus.

the presence of severe foot deformity can lead to serious pedal infections, necessitating a lower-extremity amputation.[32] Secondary osteolysis may be the prominent factor that accounts for both the spontaneous onset of neuropathic fracture and the insidious and progressive foot deformity that is the hallmark of the chronic Charcot foot.[2,33,34] Unfortunately, a threshold for pedal bone density associated with clinical outcomes after NCA has yet to be identified, and whether a BMD threshold for neuropathic fracture truly exists warrants further study.[30]

Low tarsal bone density may influence clinical decision making. The method and length of the immobilization, the weight-bearing status during immobilization and the period immediately after healing, the need for future bracing, and the selection of therapeutic footwear, inserts, and shoe modifications can be affected by low BMD, resulting in an elevated fracture risk. The rehabilitation specialist should use caution when returning individuals with a recently healed NCA and low pedal BMD to full weight bearing in order to prevent recurrence of NCA.

Another consideration is the long-term necessity for assistive devices, bracing, and therapeutic footwear to prevent future foot deformities, which must be addressed long after resolution of the acute inflammatory stage of the arthropathy. In some cases where surgery is required, the rapid loss in bone mass may influence the operative decisions of the orthopedic surgeon specialist and perhaps the outcomes of patients in the postoperative stage. Prolonged delays in fracture healing can result in high nonunion or malunion rates.[2,5,35] Similarly, a reduction in bone mass could influence the method of surgical fixation. The use of internal fixation devices may be compromised by low bone mass.[35] The use of external fixation and strict non–weight bearing may be required for extended periods of time and may well be a necessary alternative to the use of internal fixation devices. In some cases of traumatic dislocation and displaced fractures, a prolonged inflammatory stage with accompanying bone loss may delay surgical stabilization efforts, resulting in further delays in arthropathy healing.[5,35]

The National Osteoporosis Foundation estimates that 28 million Americans have osteoporosis from primary and secondary bone loss, resulting in approximately 1.5 million fractures of the spine and extremities annually.[36] It is not known whether these estimates include individuals with DM and PN. Individuals with chronic DM, PN, and NCA of the foot have profound regional bone loss, resulting in an elevated risk of neuropathic foot fracture. The average T-score of the involved foot in our subjects with NCA was -1.8 standard deviations below that of a young, adult female reference population (Fig. 2). According to World Health Organization criteria, individuals with BMD values in this range are classified with osteopenia.[37] The National Osteoporosis Foundation recommends that drug therapy be initiated for all patients with T-scores of -1.5 or lower.[36] Early reports[38–40] suggest that bone antiresorptive agent (eg, intravenous pamidronate—a bisphosphonate) administered early in the acute inflammatory phase of NCA improved healing outcomes. Newer bone anabolic agents[41] with or without bisphosphonate therapies have not yet been reported for NCA but hold great promise as pharmacological therapies in concert with traditional off-loading therapies.

At the least, all individuals with DM and PN should be routinely assessed and therapeutic strategies to arrest secondary osteolysis should be instituted to prevent the bony and joint deformities that form the hallmarks of the chronic Charcot foot.[42,43] Assessing or screening for pedal bone loss using QUS[42] or DXA[43] can be readily accomplished for individuals with DM, PN, and NCA, who are at high risk for lower-extremity amputation.

Conclusion

Pedal NCA is a well-known complication of chronic DM and PN; however, the inflammation and the associated osteolysis have been largely underappreciated by many rehabilitation specialists. Individuals with chronic NCA of the foot have an exaggerated and prolonged inflammation that may combine with other factors such as DM or PN to induce a regional osteolysis compared with age-, sex-, and race-matched controls without diabetes. This rapid and profound osteolysis can result in an elevated fracture risk and may contribute to the insidious and progressive foot deformity that is the hallmark of the chronic Charcot foot.

References

1 Sinacore DR, Withrington NC. Recognition and management of acute neuropathic (Charcot) arthropathies of the foot and ankle. *J Orthop Sports Phys Ther.* 1999;29:736–746.

2 Thompson RC, Clohisy DR. Deformity following fracture in diabetic neuropathic osteoarthropathy. *J Bone Joint Surg Am.* 1993;75:1765–1773.

3 Jordan WR. Neuritic manifestations in diabetes mellitus. *Arch Intern Med.* 1936;57:307–310.

4 Sinacore DR. Acute Charcot arthropathy in patients with diabetes mellitus: healing times by foot location. *J Diabetes Complications.* 1998;12:287–293.

5 Eichenholtz SN. *Charcot Joints.* Springfield, Ill: Charles C Thomas, Publisher; 1966.

6 Diamond JE, Mueller MJ, Delitto A, Sinacore DR. Reliability of diabetic foot evaluation. *Phys Ther.* 1989;69:797–802.

7 Armstrong DG, Lavery LA. Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry. *J Rehabil Res Dev.* 1997;34:317–321.

8 Hologic Review. The Sahara Clinical Bone Sonometer: clinical use of T- and Z-scores. Available at: www.hologic.com. Accessed June 1, 2005.

9 Greenspan SL, Bouxsein ML, Melton ME, et al. Precision and discriminatory ability of calcaneal bone assessment technologies. *J Bone Miner Res.* 1997;12:1303–1313.

10 Sinacore DR, Koger RC, Villareal DT, Strube MJ. Precision of serial quantitative ultrasonometry measures of the calcaneus [Abstract]. 2003. Available at: http://www.ptresearch.org/articles.htm.

11 DeLaet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporosis Int.* 2005;16:1330–1338.

12 Obesity: preventing and managing the global epidemic. In: *Report of a WHO Consultation on Obesity, June 3-5, 1997.* Geneva, Switzerland: World Health Organization; WHO/NUT/NCD/98.1, i-xv, 1–276, 1998. Available at: http://dosei.who.int/uhtbin/cgisirsi/Wed+Nov+21+23:21:20+MET+2001/0/49. Accessed March 18, 2007.

13 Mundy GR. Osteoporosis and inflammation. *Nutr Rev.* 2007;65:S147–S151.

14 Whiteside GT, Boulet JM, Sellers R, et al. Neuropathy-induced osteopenia in rats is not due to a reduction in weight borne on the affected limb. *Bone.* 2006;38:387–393.

15 Goldring SR, Gravallese EM. Mechanisms of bone loss in inflammatory arthritis: diagnosis and therapeutic implications. *Arthritis Res.* 2000;2:33–37.

16 Kroot EJ, Nieuwenhuizen MG, de Waal Malefijt MC, et al. Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. *Arthritis Rheum.* 2001;44:1254–1260.

17 Compston JE, Vedi S, Croucher PI, et al. Bone turnover in non-steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1994;53:163–166.

18 Krempien B, Vulkicevic S, Vogel M, et al. Cellular basis of inflammation induced osteopenia in growing rats. *J Bone Miner Res* 1988;3:573–582.

19 Armour KJ, Armour KE, van't Hof RJ, et al. Activation of the inducible nitric oxide synthase pathway contributes to inflammation induced osteoporosis by suppressing bone formation and causing osteoblast apoptosis. *Arthritis Rheum.* 2001;44:2790–2796.

20 Young MJ, Marshall A, Adams JE, et al. Osteopenia, neurological dysfunction and the development of Charcot neuroarthropathy. *Diabetes Care.* 1995;18:34–38.

21 Geusens P, Dequeker J, Verstraeten A, Nijs J. Age-, sex-, and menopause-related changes of vertebral and peripheral bone: population study using dual and single photon absorptiometry and radiogrammetry. *J Nucl Med.* 1986;27:1540–1549.

22 Krolner B, Nielsen P. Bone mineral content of the lumbar spine in normal and osteoporotic women: cross-sectional and longitudinal studies. *Clin Sci.* 1982;62:329–336.

23 Maluf KS, Mueller MJ. Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers. *Clin Biomech (Bristol, Avon).* 2003;18:567–575.

24 LeMaster JW, Mueller MJ, Reiber GE, et al. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: Feet First randomized controlled trial. *Phys Ther.* 2008;88:1385–1398.

25 Deshpande AD, Dodson EA, Gorman I, Brownson RC. Physical activity and diabetes: opportunities for prevention through policy. *Phys Ther.* 2008;88:1425–1435.

26 Armstrong DG, Lavery LA. Acute Charcot's arthropathy of the foot and ankle. *Phys Ther.* 1998;78:74–80.

27 McCrory JL, Morag E, Norkitis AJ, et al. Healing rates of Charcot fractures: skin temperature and radiographic correlates. *The Foot.* 1998;8:158–165.

28 Piaggesi A, Rizzo L, Golia F, et al. Biochemical and ultrasound tests for early diagnosis of active neuro-osteoarthropathy (NOA) of the diabetic foot. *Diabetes Res Clin Pract.* 2002;58:1–9.

29 Commean PK, Ju T, Liu L, et al. Tarsal and metatarsal bone mineral density using volumetric quantitative computed tomography. *J Digitial Imaging.* In press.

30 Prior F, Commean PK, Ju T, et al. Developing a biomarker for neuropathic arthropathy in diabetic patients. Life Science Systems and Applications Workshop, 2007. LISA 2007. IEEE/NIH. November 8–9, 2007. IEEE Xplore. Available at: http://ieeexplore.ieee.org/xpl/RecentCon.jsp?punumber=4400868&conhome=1001257.

31 Mueller MJ, Zou D, Bohnert KL, et al. Plantar stresses on the neuropathic foot during barefoot walking. *Phys Ther.* 2008;88:1375–1384.

32 Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care.* 1990;13:513–521.

33 Sinacore DR. Severe sensory neuropathy need not precede Charcot arthropathies of the foot or ankle: implications for the rehabilitation specialist. *Physiother Theory Pract.* 2001;17:39–50.

34 Sinacore DR, Bohnert KL, Hastings MK, Johnson JE. Mid foot kinetics characterize structural polymorphism in diabetic foot disease. *Clin Biomech (Bristol, Avon).* 2007 June 27. [Epub ahead of print.]

35 Johnson JE. Charcot neuropathy of the foot: surgical aspects. In: Bowker JH, Pfeifer MA, eds. *Levin & O'Neal's The Diabetic Foot.* 6th ed. St Louis, Mo: Mosby Inc; 2001:587–606.

36 *Physician's Guide to Prevention and Treatment for Osteoporosis.* Washington, DC: National Osteoporosis Foundation; 2003.

37 Kanis JA, and the WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. *Osteoporosis Int.* 1994;4:368–381.

38 Guis S, Pellissier JF, Arniaud D, et al. Healing of Charcot's joint by pamidronate infusion. *J Rheumatol.* 1999; 26:1843–1845.

39 Jude EB, Selby PL, Burgess J, et al. Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomized controlled trial. *Diabetologia.* 2001;44:2032–2037.

40 Anderson JJ, Woelffer KE, Holtzman JJ, Jacobs AM. Bisphosphonates for the treatment of Charcot neuroarthropathy. *J Foot Ankle Surg.* 2004;43:285–289.

41 Gasser JA. The relative merits of anabolics versus anti-resorptive compounds: where our targets should be, and whether we are addressing them. *Curr Opin Pharmacol.* 2006;6:313–318.

42 Hastings MK, Sinacore DR, Fielder FA, Johnson JE. Bone mineral density during total contact cast immobilization for a patient with neuropathic (Charcot) arthropathy. *Phys Ther.* 2005;85:249–256.

43 Herbst SA, Jones KB, Saltzman CL. Pattern of diabetic neuropathic arthropathy associated with the peripheral bone mineral density. *J Bone Joint Surg Br.* 2004;86:378–383.