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Persistent inflammation with pedal osteolysis 1 year after Charcot neuropathic osteoarthropathy

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ABSTRACT

Aims: To determine local and systemic markers of inflammation and bone mineral density (BMD) in the foot and central sites in participants with diabetes mellitus and peripheral neuropathy (DMPN) with and without acute Charcot neuropathic osteoarthropathy (CN).
Methods: Eighteen participants with DMPN and CN and 19 participants without CN had foot temperature assessments, serum markers of inflammation [C-reactive protein, (CRP) and erythrocyte sedimentation rate, (ESR)] and BMD of the foot, hip and lumbar spine at baseline and 1 year follow-up.
Results: CN foot temperature difference was higher compared to DMPN controls at baseline (4.2 ± 1.9 °F vs. 1.2 ± 0.9 °F, $P < 0.01$) and after 1 year (2.9 ± 3.2 °F vs. 0.9 ± 1.1 °F, $P < 0.01$). Serum inflammatory markers in the CN group were greater at baseline and remained elevated 1 year later compared to DMPN controls (CRP, $P = 0.02$, ESR, $P = 0.03$). All pedal bones' BMD decreased an average of 3% in the CN foot with no changes in hip or lumbar spine. DMPN controls' foot, hip and lumbar spine BMD remained unchanged.
Conclusions: Local and systemic inflammation persists 1 year after CN with an accompanying pedal osteolysis that may contribute to mid foot deformity which is the hallmark of the chronic Charcot foot.

1. Introduction

Acute Charcot neuropathic osteoarthropathy (CN) is a non-infective bone and joint destruction characterized by the onset of a red, hot, swollen foot in the presence of a dulled sensation to pain impairing function, mobility and walking. Acute CN inflammation can lead to an accelerated pedal osteolysis[1] contributing to rife sequelae, most notably acquired mid foot deformity[2] that is the hallmark of the chronic Charcot foot.[3] Persistent local or systemic inflammation with osteolysis can contribute to any number of poor outcomes including plantar ulceration, infection, and ultimately lower extremity amputation.[4–6]

Acute CN has long been associated with increases in local skin temperatures.[1,7–9] Typically, skin temperature differences between feet of non-diabetic, non-neuropathic individuals vary little (e.g., ≤1.8 °F or 1 °C).[1] However, in individuals with diabetes mellitus and peripheral neuropathy (DMPN), temperature difference between active Charcot and non-active foot have been reported to range from 9.2 to 26.5 °F (5.1 to 14.7 °C).[7,8] The utility of monitoring temperature difference between Charcot and non-Charcot feet for clinical decision making is not without controversy. McCrory and colleagues questioned the utility of temperature differences to reflect the healing of acute Charcot fractures treated by total contact cast immobilization. They concluded that temperature difference may indicate a resolving inflammation, though an unreliable measure for clinical decision-making.[10] More recently, Ruotolo and colleagues showed that normalization (i.e., reduction) in skin temperature difference does not reflect the persistent bony inflammation as demonstrated by enhanced uptake of ^{18}F-FDG uptake on PET/CT scans. They concluded that skin temperature monitoring to quiescence is an insufficient and misleading clinical criteria to establish when the acute inflammatory process is completely over in pedal

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bones, therefore normalization of skin temperature difference is not a sensitive parameter to drive therapeutic decisions.[11]

Despite the recognized need for resolution of acute inflammation in CN, there also remains some controversy whether there is an accompanying systemic inflammatory response in neuropathic individuals with acute CN.[12] Petrova and colleagues reported an average increase of 5.6 °F (3.1 °C) in Charcot foot temperature in 36 consecutive patients on presentation to a diabetic foot specialty clinic. Despite the local inflammation, they observed only a small elevation in serum markers of inflammation. They found a median concentration of C-reactive protein (CRP) of 5.8 mg/l with 47% of the patients having CRP levels in the normal range (e.g., ≤5 mg/l). Additionally they reported a median serum erythrocyte sedimentation rate (ESR) concentration of 21 mm/h. which was mildly elevated.[12] These findings require confirmation including follow-up over time after resolving acute inflammation.

There have been few clinical reports directly linking inflammation to pedal osteolysis in individuals with DMPN and acute CN. In a case–control cohort study, Sinacore and colleagues reported the Charcot foot had an average 3.7 °C (6.7 °F) higher skin temperature with an 18% lower calcaneal BMD than the non-Charcot foot.[1] Petrova and Edmonds found an 8% lower calcaneal BMD in the Charcot foot compared to the non-Charcot foot at presentation prior to cast immobilization attributing the pedal osteolysis at presentation to a higher skin temperature difference of 3.5 °C (6.3 °F) in the Charcot foot.[13] In a 2013 study, Gutekunst and colleagues reported that individuals with DMPN and acute CN had a 14% and 11% lower BMD in the 2nd and 5th metatarsal, respectively, compared to an age-matched group of individuals with DMPN but without CN.[14] These few reports support the hypothesis that inflammation may have an incipient causal role in acute CN with accompanying bone loss.[15]

Several studies have reported the natural history and long-term follow-up of feet after acute CN[4,7] however, there have been no previous reports of local and systemic inflammation with pedal and central site assessments of BMD 1 year after CN. Spontaneous new and recurrent neuropathic fractures are well-documented outcomes following CN as are acquired mid foot and hind foot deformities.[2,16,17] However it is not known if osteolysis accompanies a persistent inflammation or if BMD recovers within 1 year after CN. It is possible that often reported poor clinical outcomes, complications and sequela may be related directly or indirectly to the resolution of inflammation and the recovery of pedal BMD including adequate fracture healing and bony consolidation. Similarly, it is also unclear whether local changes in pedal BMD are reflected in central BMD sites (e.g., hip and spine) that are more routinely assessed. Therefore, the purposes of this study were to: 1] determine both local and systemic markers of inflammation and BMD in feet and central sites in participants with DMPN with and without acute CN at baseline and at 1 year follow-up assessment; 2] examine the relationship between local and systemic markers of inflammation with pedal BMD at baseline and 1 year follow up. We hypothesized that local and systemic markers of inflammation would be reduced 1 year after CN onset and be similar to DMPN participants without CN and there would be no association between inflammation markers and pedal BMD. In addition, we hypothesized that foot and central site measures of BMD in CN participants would not be different 1 year after acute CN compared to baseline values due to resumption of daily weight bearing activities such as walking and standing.

2. Materials and methods

2.1. Participants

We recruited participants with DMPN with and without acute CN. Participants with DMPN without CN were recruited at Washington University School of Medicine and surrounding areas from: 1] our medical center's volunteer research participation registry, 2] recruitment notices posted throughout our medical center, 3] contacts with community orthopedic surgeons and podiatrists, or 4] from our Wound and Ostomy specialty clinic. Participants with CN were either referred from our diabetic foot specialty clinic to our physical therapy service for total contact cast (TCC) immobilization over a 36-month period or recommended for participation by community orthopedic surgeons or podiatrists. Inclusion criteria for all participants were previously diagnosed with diabetes mellitus (type 1 or type 2) and PN by a physician or were taking medications or exogenous insulin to control their blood glucose levels.[18] Participants with DMPN and CN had a physician-diagnosed CN (Eichenholtz stage 1, 2 or 3) based on a radiograph-confirmed overt fracture, bony fragmentation or neuropathic joint change (subluxation or dislocation) consistent with CN and no evidence of local infection, osteomyelitis, or advancing cellulitis. Participants with DMPN and CN were eligible if they had a concurrent plantar ulcer since in our experience plantar ulcers typically heal prior to resolution of inflammation of acute CN.[19] Exclusion criteria for all DMPN participants were body weight greater than 350 lb (DXA and CT scanner's weight limit), partial or complete foot amputation of tarsal and metatarsal bones and a history or active evidence of osteomyelitis. Participants with DMPN without CN were excluded for any history or current foot disease including pedal ulceration, fracture or fixed mid foot or hind foot deformities; history of foot or leg trauma, metabolic bone disease, kidney or liver disease or transplant, taking immunosuppressive medications, women on oral contraceptives, bone anti-resorptive agents or hormone replacement therapy.

Participant demographics were obtained by self-report at the time of the baseline visit. The average duration of time prior to seeking therapy for their CN was determined by participant interview and report. Each participant's body weight was measured on a calibrated balance scale and height measured using a scale-mounted stadiometer without shoes. All participants read and signed an informed consent outlining our research protocol. Our research protocol was approved by our Human Subjects Research Protection Office's institutional review board. Each participant was reimbursed a modest sum after each research data collection visit.

2.2. Peripheral Neuropathy(PN)

All participants were diagnosed with PN prior to enrollment in the study. PN was defined as inability to sense light touch (pressure) at any one of 7 locations on the foot (dorsal mid foot, plantar surface of the first, third, fifth metatarsal heads; medial and lateral mid foot and central hind foot) using a single-thickness (5.07/10-g) Semmes–Weinstein monofilament[1,20,21] or a vibration perception threshold (VPT) ≥ 25 V at the great toe with the Biothesiometer (BioMedical Instrument Co, Newbury OH).[20]

2.3. Foot skin temperatures

To confirm the presence of local foot inflammation, all participants had skin temperatures assessed with infrared dermal thermometry (Exergen Dermatemp DT1001-LN) at the same 7 standard locations on each foot including the CN location at baseline and 1 year.[1] Participants were asked to remove socks, hose and footwear and rest comfortably on an examination table for at least 15 min in a temperature controlled room. We performed 3 trials of skin surface temperature assessment at each location in a standardized, ordered sequence.[1] 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 foot without CN was subtracted from the CN foot and considered the measured skin temperature.

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