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REVIEW ARTICLE

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Charcot neuroarthropathy in persons with diabetes: It's time for a paradigm shift in our thinking

Dane K. Wukich[1] | Robert G. Frykberg[2] | Venu Kavarthapu[3,4,5]

[1]University of Texas Southwestern Orthopaedic Surgery, Dallas, Texas, USA

[2]Podiatric Medicine, Midwestern University Glendale, Glendale, Arizona, USA

[3]Orthopaedic Surgeon – King's College Hospital, London, UK

[4]Orthopaedic Lead, King's Diabetic Foot Unit, London, UK

[5]University of Southern Denmark, Odense, Denmark

Correspondence
Dane K. Wukich, 1801 Inwood Rd, Dallas, TX 75390, USA.
Email: Dane.wukich@utsouthwestern.edu

Abstract

The aim of this paper is to review the recent literature regarding the epidemiology and surgical management of Charcot neuro-osteoarthropathy (CNO). We propose that a fundamental change in the approach and assumptions regarding the historical treatment of active CNO should be considered. Although the true incidence and prevalence of CNO in the US population with diabetes are not known, we estimated the incidence to be 27,602 per year and the prevalence to be 208,880 persons. In persons with diabetes, the incidence of CNO is higher than that of prostate, lung, kidney, and thyroid cancer, and in the entire US population, the incidence of CNO is higher than that of multiple myeloma, soft tissue sarcoma, and primary bone sarcoma. In persons with diabetes, the incidence of CNO is higher than fractures of the femoral shaft, distal femur, tibia, talus, calcaneus and Lisfranc ligament injuries. Surgical techniques have evolved over the past half century, and surgery is the standard for treating displaced fractures and intra-articular injuries. Since CNO is a fracture, dislocation, or fracture dislocation in patients with neuropathy, why do we treat CNO differently? Elsewhere in the skeleton displaced osseous and ligament injuries are treated surgically. Based on the information presented in this manuscript, we suggest that it is time for a paradigm shift in the treatment of persons with CNO. While uncommon, CNO in persons with diabetes is not rare. Given the advances in surgical techniques, surgical intervention should be considered earlier in persons with CNO who are at risk for developing deformity related foot ulceration.

KEYWORDS
charcot, diabetes, epidemiology, incidence, neuroarthropathy, prevalence

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1 | INTRODUCTION

Jean-Martin Charcot's contributed to the understanding of Charcot neuro-osteoarthropathy (CNO) by linking CNO to the central nervous system in patients with tabes dorsalis. In 1966, Harris and Brand[1] noted that the anaesthetic foot and ankle were warmer than the foot and ankle in patients with intact sensation, and that warmth was the earliest sign of breakdown. Subsequently, inflammation and injury were linked to the pathogenesis of CNO. In 1966, Eichenholtz[2] described three stages of CNO: development, coalescence, and reconstruction. The following year Johnson[3] reported on the association of neuropathic fractures and dislocations in the pathogenesis of CNO. Fractures and dislocations in patients with marked sensory impairment resulted in bone or joint damage typical of CNO. These changes included swelling, warmth, ligament laxity, and subluxation in patients with little or no pain. Johnson's described high rates of complications after surgically treating these injuries, including infection, pseudarthrosis, and hardware failure. Johnson also opined that the role of fractures and dislocations in the pathogenesis of neuropathic joints (i.e., CNO) had been largely ignored. His use of the term neuropathic joint was synonymous with his description of Charcot joints. In the majority of his 118 cases, he concluded that fractures, sprains, and repetitive trauma were involved in the pathogenesis of the neuropathic changes (i.e. CNO). He further stated that inadequately treated fractures, sprains, and joint effusions were the precursors of neuropathic joint destruction. Advances in imaging modalities over the past several decades, such as MRI and CT scans, have confirmed Johnson's observation from more than 55 years ago that CNO is a disease that affects bones, ligaments, and joints. Subsequently Shibata et al.[4] i introduced the concept of Stage 0 Charcot, characterised by signs of acute inflammation (oedema, warmth, redness) with minimal or absent radiographic changes. Unfortunately, patients rarely present to knowledgeable providers during Stage 0, a period when offloading can reverse the process without distortion of osseous architecture. Regrettably, patients who present with an acutely inflamed foot are often misdiagnosed as having cellulitis, gout, or deep vein thrombosis because of “normal” radiographs. Consequently, patients ambulate on a vulnerable foot, leading to deformity.[5] During this active stage of “normal” radiographs, MRI demonstrates bone oedema, bone bruising, stress fractures without cortical disruption, soft tissue oedema, joint subluxation, cartilage damage and joint effusion.[6] Petrova et al.[7] studied patients treated with offloading and cast immobilisation and found that bone mineral density (BMD) of the active CNO foot was significantly reduced compared with that of the non-CNO contralateral foot at presentation. A further significant decline in BMD occurred from its presentation until resolution, most pronounced during the first three months of treatment. Other authors have disputed the observation that patients with diabetes and CNO have osteoporosis in the skeleton in general or in the CNO affected foot more frequently than patients with diabetes but without CNO.[8]

Although the role of inflammation in the pathogenesis of CNO was introduced by others, further understanding was gained by the role of proinflammatory cytokines in the activation of osteoclasts.[1,3,9–11] Although there is a profound local inflammatory response in CNO, systemic signs of inflammation are absent.[12] The role of RANKL in activating osteoclastic precursors has demonstrated the importance of inflammation and bone resorption. Similar mechanisms have been observed in cancer related bone resorption, Paget's disease, and osteoporosis. Jeffcoate, as Johnson had inferred decades earlier, proposed that active CNO represented an exaggerated inflammatory response to trauma, whether the trauma was minor or major.[3,13] The abnormal inflammatory response and continued load bearing on the foot due to loss of protective sensation results in further bone fragmentation, deformation, and instability. Recent guidelines and a systemic review of CNO in persons with diabetes have been published, which provide contemporary thinking on the management of active CNO.[14–16]

Historically, non-surgical treatment has been the cornerstone of care for most CNO deformities. Active CNO is typically managed in a total contact cast and with weight bearing limitation until it progresses to the inactive phase. Recently, there has been enthusiasm for surgical management to address chronic (inactive) Charcot foot deformities.[9,17] However, active CNO presentations, even with displaced and unstable fractures, are currently managed with cast immobilisation in most units. Nowhere else in the axial or appendicular skeleton are displaced fractures and dislocations treated nonsurgically. Intra-articular fractures with subtle displacement of ≥2 mm undergo anatomic reduction and fixation in most major joints, including the upper and lower extremities. During the 1960's when Harris and Brand, Eichenholtz, and Johnson published their seminal work, surgeons routinely treated fractures of the femur, tibia, and ankle with closed reduction and casting.[3,18–23] With improvement in surgical techniques, these fractures are now treated with anatomic reduction and internal fixation to restore normal anatomy. Ankle fractures in persons with diabetes and neuropathy can serve as a surrogate for CNO based upon similar pathophysiology. Non-surgical treatment of unstable, ankle fractures results in devastating outcomes including high rates of ulceration, malunion, infection, and amputation.[24–26] Given that the overwhelming majority of surgeons who treat fractures would not treat a displaced ankle fracture in persons with diabetes non-surgically, why do we treat fractures and dislocations of the foot and ankle in patients with active CNO differently in the majority of cases? One reason is that CNO has been thought of as a largely non-surgical problem due to disastrous complications with surgery many years ago.[3] Caution has been advised against surgery during the acute inflammatory stage due to perceived high rates of adverse outcomes. In 2004, Pinzur[27] wrote that “a review of current standard orthopaedic textbooks reveals almost universal agreement that active CNO should be treated nonsurgically with a total contact cast and that long-term care should be accommodative with various orthotic methods. Historically, surgery has been advised when accommodative treatment has failed.” To the best of our knowledge, there are no controlled studies, either retrospective or prospective, that support this bias. Additionally, surgical intervention in patients with CNO was avoided because of the potential for vascular compromise, resulting in impaired wound healing. It is now recognized that patients with CNO usually have adequate perfusion to successfully undergo surgical reconstruction.[28] While peripheral artery disease is not uncommon in patients with chronic or inactive CNO, critical limb ischaemia and the need for revascularisation are significantly less likely in Charcot patients compared to patients with diabetic foot ulcers.[28]

The aim of this paper is to review the recent literature regarding the epidemiology and surgical management of CNO. We propose that a fundamental change in the approach and assumptions regarding the historical treatment of active CNO should be considered. Based on the information presented in this manuscript, we suggest that it is time for a paradigm shift in the treatment of persons with CNO.

2 | EPIDEMIOLOGY OF CHARCOT NEUROARTHROPATHY IN PERSONS WITH DIABETES

The true incidence and prevalence of Charcot neuroarthropathy in persons with diabetes are not known; however, several studies have reported the rates from selected countries and regions. O'Loughlin et al.[29] reported a prevalence of 0.26% (40 CNO patients/15,608 persons with diabetes) from southeast Ireland but did not report the incidence. Similarly, Metcalf et al.[30] reported a prevalence of 0.04% (90 CNO cases/205,033 persons with diabetes) in the East Midlands of England and did not report the incidence. The lower prevalence of CNO in Metcalf's study is likely to be due to the nature of their study as they included patients with active CNO who were seen at specialty diabetic foot clinics during a one-month period (April 2017), while O'Loughlin's study included patients over a six-year period. Lavery et al.[31] reported an overall incidence of 8.5 per 1000 (0.85%) per year, with non-Hispanic whites (11.7/1000) having higher rates of CNO than Mexican Americans (6.4/1000). While Cofield's study in 1983 reported an incidence of 29%, his series was not population based and the data were taken from a clinical trial of patients with established neuropathy.[32] Anichini et al.[33] reported a yearly incidence rate of around 12 per 100,000 of active Charcot foot in the period 2008–2010 and between 9.8 and 3.4 in 2013–2015, determined from hospital admission data in Tuscany. This study was potentially biased because they only studied patients who were admitted to the hospital in a population-based national study. Svendsen et al.[34] retrieved patient records over a 23-year period (1995–2018) from the Danish National Patient Register, which contains information on hospitalisation, outpatient visits, and emergency department visits. The authors reported the incidence rate of Charcot foot to be 7.4 per 10,000 (0.074%) person-years and the prevalence to be 0.56% among people with diabetes (of 309,557 individuals with an ICD-10 diagnosis of diabetes, 1722 were diagnosed with Charcot foot). It is the largest population-based study to investigate the epidemiology of CNO and data from this robust study provides an opportunity to estimate the prevalence and incidence of CNO in the United States. According to the Centers for Disease Control and Prevention (CDC) an estimated 11.3% of the US Population (330,086,498) has diabetes, equating to 37,300,000 persons with diabetes.[35] Using Svendsen's statistics for the US population, the estimated incidence of CNO in persons with diabetes would be 27,602 persons per year (0.00074 times 37,300,000) and the prevalence would be 208,880 persons with diabetes living with CNO.

To put this in perspective, it is helpful to review the incidence of certain primary malignancies in comparison with CNO.[36,37] Table 1 demonstrates the incidence of CNO compared with primary malignancies and de novo metastatic disease. The five malignancies that were chosen are the five classic primary malignancies that metastasise to bone (breast, prostate, lung, kidney, thyroid) as well malignancies commonly treated by orthopaedic oncologists (myeloma, soft tissue sarcoma, primary bone sarcoma). Compared to CNO (27,602 new cases per year), the only primary malignancies cited that have higher incidence rates in persons with diabetes are breast cancer (47,781 new cases per year) and prostate cancer (40,657 cases per year).

Patients with de novo bone metastases, diagnosed between 2010 and 2015, were abstracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme.[38] The incidence rate of cancer patients across all age groups with de novo bone metastases was 18.8 per 100,000 (0.0188%). Like CNO patients, the average and median age of all participants with de novo bone metastasis was 67.0 years and most patients included in the analyses were male (N = 59,681, 57.8%). As expected, the incidence of bone metastases increases with each decade of life, with an incidence of 0.9 per 100,000 during ages 25–29 years to 108 per 100,000 during ages 75–79 years Table 1 illustrates the overall incidence rates of de novo bone metastases as well as the incidence rates of the top ten malignancies with de novo bone metastases. The incidence of CNO in patients with diabetes is higher than any individual type of de novo bone metastasis in patients with diabetes (11.3% of US population) except for metastases from cancer of the lung and bronchus (Table 1).

A recent systemic review by Ponkilainen et al. reported the incidence of musculoskeletal injuries in the general population.[39] Table 2 reflects the incidence of lower extremity injuries, and the only injuries that had a higher incidence than our estimated incidence of CNO (0.074%) were hip fractures (0.113%), ankle fractures (0.094%) and all combined foot fractures of the hindfoot, midfoot and forefoot (0.091%). Charcot neuroarthropathy had a higher incidence than metatarsal fractures, toe fractures, pelvic fractures, proximal tibia fractures, tibia shaft fractures, patellar fractures, femoral shaft fractures, Lisfranc Injuries, calcaneus fractures, and distal femur fractures. The Rasmussen study, included in the aforementioned systematic review, reported in more detail on the population-based incidence and epidemiology of 5912-foot fractures (Table 2).[40] In this study confirmed forefoot fractures (metatarsal and toes) were the most common fractures of foot followed by hindfoot and midfoot fractures. Based on these population-based data the incidence of fractures in the diabetic population in the USA can be estimated by multiplying the population incidence with 11.3% (prevalence of diabetes in the US population). The estimated incidence of CNO

TABLE 1 This table illustrates the rates of cancer in the whole US population and in patients with diabetes mellitus (11.3% of the population).

	Cases per 100,000	Incidence (%)	New cases per year entire US population	New cases per year in persons with diabetes (11.3%)
Primary malignancies				
Breast	128.1/100,000	0.128%	422,843	47,781
Prostate	109.9/100,000	0.109%	359,796	40,657
Charcot	74/100,000	0.074%	n/a	27,602
Lung	56.3/100,000	0.0563	185,839	20,999
Kidney	17.3/100,000	0.0173	57,105	6452
Thyroid	13.8/100000	0.0138	45,552	5147
Myeloma	7/100,000	0.007%	23,106	2611
Soft tissue sarcoma	4/100,000	0.004%	13,400	1492
Primary bone sarcoma	1.2/100,000	0.00123%	3970	449
Osteosarcoma	0.3/100,000	0.0003%	1000	113
Hodgkin's lymphoma	2.6/100,000	0.0026	8582	970
De Novo Bone Metastatic Disease	**Cases per 100,000**	**Incidence (%)**	**Total US Population 330,088,496**	**Patients with Diabetes (11.3%)**
Overall	18.8	0.0188%	62,057	7012
Lung and bronchus	8.94	0.0094%	31,028	3506
Prostate	2.85	0.0029%	9573	1082
Breast	2.42	0.0024%	7922	895
Kidney	0.82	0.0008%	2641	298
Colon and rectum	0.45	0.0005%	1650	186
The pancreas	0.42	0.0004%	1320	149
Liver and bile duct	0.37	0.0004%	1320	149
Oesophagus	0.30	0.0003%	990	119
Stomach	0.29	0.0003%	990	119
Bladder	0.27	0.0003%	990	119

(0.074%) in patients with diabetes is higher than the incidence of hindfoot (0.014%) and midfoot (0.007%) fractures but lower than overall foot fractures (0.142%) and forefoot fractures (0.124%) in the general population. In patients with diabetes, the estimated number of new cases of ankle, hindfoot, midfoot and forefoot CNO per year (27,602) will be higher than any lower extremity injury except for forefoot fractures (46,252), hip fractures (42,112), and ankle fractures (35,062) (Figure 1).

3 | THE SURGICAL MANAGEMENT OF CHARCOT NEUROARTHROPATHY IN PERSONS WITH DIABETES

Over the past four decades, surgical fixation techniques have evolved and been refined. The introduction of internal fixation by the AO group (Association for the Study of Osteosynthesis) several decades ago introduced fracture and reconstructive surgeons to biomechanically sound plates and screws.[41] Intramedullary devices were developed to stabilise long bone fractures, changing the management of polytrauma patients.[42] The concept of circular external fixation as developed by Ilizarov was used to treat complex foot and ankle fractures.[43] Surgeons now have access to robust constructs of internal fixation, external fixation, and even hybrid methods of fixation. Charcot specific implants have been designed explicitly for use in patients with CNO to withstand high ground reactive forces in persons with neuropathy. These implants are made of titanium or stainless steel and have undergone rigorous biomechanical testing.[44] Although only a small series of patients have been reported, surgery during the active phase has been found to be successful.[17,45] The role of the multidisciplinary team (MDT) approach in the surgical management of Charcot foot deformities is well understood. Ankle fractures and dislocations in persons with diabetes and neuropathy are surgically treated during the acute phase, so why not foot

TABLE 2 This table illustrates rates of lower extremity fractures in the US population and in patients with diabetes mellitus (11.3% of the population).

Incidence of lower extremity fractures[39]	Incidence	Incidence (%)	Total US population 330,088,496	Diabetes (11.3%) 37,300,000
Hip fracture	112.9/100.000	0.113%	372,670	42,112
Ankle fracture	94/100,000	0.094%	310,283	35,062
Foot (entire) fractures	91.2/100,000	0.091%	301,041	34,018
Charcot	74/100,000	0.074%	n/a	27,602
Metatarsal fractures	71.2/100,000	0.071%	234,363	26,483
Toe fractures	55.5/100,000	0.056%	183,199	20,702
Pelvic fractures	33/100,000	0.033%	108,929	12,309
Tibia fractures (shaft)	20.8/100,000	0.028%	92,425	10,444
Tibia fractures (proximal)	22.5/100,000	0.023%	74,270	8393
Patellar fracture	13.4/100,000	0.013%	44,232	4998
Femoral shaft	12.2/100,000	0.012%	40,271	4551
Lisfranc injuries	11.4/100,000	0.011%	36,310	4103
Calcaneus fracture	10/100,000	0.010%	33,009	3730
Femur fractures (distal)	8.4/100,000	0.008%	27,727	3133
Population-based incidence and epidemiology of 5912-foot fractures[40]	**Incidence**	**Incidence (%)**	**Total US Population 330,088,496**	**Diabetes (11.3%) 37,300,000**
Overall foot fractures	142.3/100,000	0.142%	468,723	52,966
Forefoot	123.9/100,000	0.124%	409,310	46,252
Charcot	74/100,000	0.074%	n/a	27,602
Hindfoot	13.7/100,000	0.014%	46,212	5222
Midfoot	6.5/100,000	0.007%	23,106	2611

Note: The lower part of the figure concentrates on fractures of the foot and ankle.

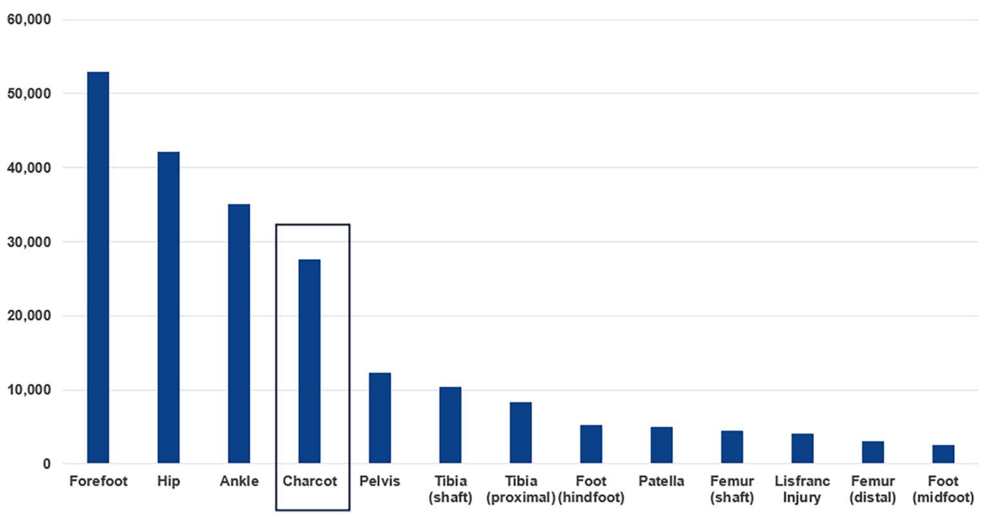

FIGURE 1 This figure illustrates the rates of lower extremity fractures in patients with diabetes.

Charcot fractures and dislocations? Many variables play a role in achieving successful outcomes in foot fracture fixation or deformity correction surgery in this challenging patient population. Based on the authors' experience, it is prudent to address several important aspects in patients with active CNO foot or ankle prior to surgical intervention. Oedema associated with active CNO can be reduced with total contact casting or compression management. Optimal perioperative glycaemic management is vital to reduce the rate of surgical site infection, and co-management of these patients with hospitalists experienced inpatient diabetes management is crucial. In some cases, delaying surgery until improvement in the HbA1c is advisable since most active CNO does not immediately place the soft tissues at risk. Despite being obese, many diabetic patients are malnourished, and nutritional consultation can be invaluable to improve wound healing. Vitamin D deficiency is extremely common, and restoration of normal levels can help to improve fracture and fusion healing. Finally, the cessation of tobacco products is a high priority due to the negative impact on the soft tissue and osseous healing. Despite these proactive approaches, many patients have underlying renal disease and other co-comorbidities which increase complication rates and cannot be reversed (e.g., neuropathy).

It has been well established that surgical complications are common in Charcot patients, including wound-related problems, infection, hardware failure, non-union, and even amputation.[46] However, the reduction of deformity is never easier than during the active phase. Arthrodesis is technically less difficult at that time because complex multiplanar osteotomies that are performed during reconstructions are not required to realign and expose the involved joints. Why wait until the foot/ankle consolidates in a non-plantigrade position, if surgical intervention in the active phase can result in easier restoration of anatomic alignment, reduced the length of surgery, and ultimately better outcomes?

Without question, some cases of CNO can be successfully managed nonsurgically. However, ankle and hindfoot CNO can be more difficult to manage non-surgically as the soft tissues overlying the medial and lateral malleoli have little tolerance for varus and valgus deformities. Pinzur[27] reported on his personal series of 147 patients with midfoot CNO, and in patients with a plantigrade foot at presentation, 59% achieved a satisfactory outcome without surgery. For the purposes of his study, a satisfactory outcome was defined as long-term management with standard, commercially available, therapeutic shoes, and custom-fabricated accommodative foot orthoses. In 2005, Saltzman et al.[47] reviewed the experience of an intensive nonoperative initial treatment programme at the University of Iowa. The authors reported a 2.7% annual rate of amputation, a 23% risk of requiring bracing for more than 18 months, and a 49% risk of recurrent ulceration. Their conclusion was that improved methods of care were needed for CNO in patients with diabetes. The difficulty arises in determining which cases will consolidate in a non-plantigrade foot that risks the loss of the skin integrity. Traditionally, a foot with CNO deformity that can be accommodated in therapeutic shoes and with accommodative foot orthoses shoe wear has been considered a satisfactory result. Persons with diabetes need to exercise to promote cardiovascular fitness, maintain optimal weight, improve long-term glycaemic control, and maintain a satisfactory health related quality of life (HRQOL). How can we recommend simple fitness measures such as walking in patients with a neurologically impaired deformed foot? Intuitively, we know that a greater number of steps taken correlates with increasing plantar and shear stress, heralding the risk of skin breakdown. Surgeons treat fractures and dislocations to *prevent* future problems such as traumatic arthritis, deformity, and loss of function. HRQOL in Charcot patients is severely impacted; therefore, why not try to improve HRQOL by striving for anatomic reduction, stabilisation, and preservation of function?.[48,49] Why don't we treat this injury (perceived or non-perceived) like it really is, a neuropathic fracture, dislocation, or fracture-dislocation, just as Johnson aptly named it more than fifty years ago? Why not treat this injury as it would be treated elsewhere in the spine, upper extremity, or lower extremity? The indications for surgical intervention in patients with non-neuropathic fractures and dislocations of the ankle, hindfoot, midfoot and forefoot include residual incongruity, unstable injuries, and a non-anatomic reduction of closed injuries. Only truly non-displaced injuries (<2 mm of displacement and no angular malalignment) are treated non-surgically elsewhere in the body. In persons with diabetes and neuropathy, we routinely accept deformities of the foot and ankle that would not be accepted in patients without neuropathy. Although technically challenging, consideration should be given to treating active CNO like all other fractures and dislocations in an MDT setup with early surgery to restore anatomy and prevent late sequelae. The goal in treating Charcot patients is to maintain HRQOL, prevent ulceration and prevent amputation. To achieve this aim, early recognition and intervention is mandatory. By preventing deformity, we can prevent CNO related foot ulcers, infection, and amputations (Figure 2). It has been estimated that 85% of diabetes-related amputations are preceded by a foot wound and more than 99% of foot infections in persons with diabetes are related to a foot wound.[50] Prevention of the foot wounds will prevent soft tissue and osseous pedal infections and therefore reduce the rate of amputation. The overwhelming majority of Charcot patients do not undergo amputation because of critical limb ischaemia, but rather because of infected foot wounds secondary to deformity. Sohn's study clearly illustrates this point as the risk of amputation is 12 times greater in

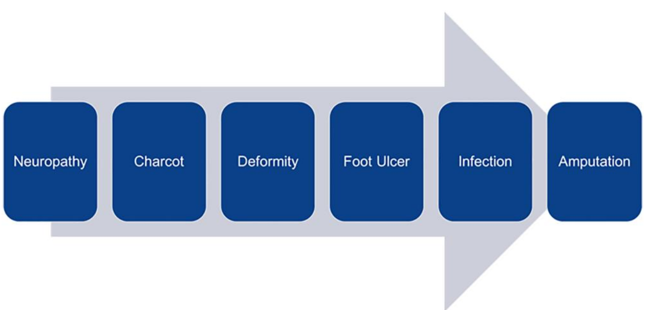

FIGURE 2 The figure illustrates the pathway to amputation in patients with CNO.

CNO patients with a foot ulcer compared with CNO patients without a foot ulcer.[51] Another study demonstrated a six-fold increase in amputations in CNO patients presenting with wounds compared with patients without wounds.[52] Going forward, a paradigm shift is necessary in our treatment algorithm of neuropathic fractures and dislocations in patients with diabetes-related neuropathy. These patients deserve to be treated like all other patients with similar injuries, so that HRQOL can be maintained in this high-risk population. Although all of these patients have neuropathy, we should concentrate on the "fracture and/or dislocation" with the goal of restoring anatomy, stability, and function. Because of the stress that neuropathic patients may unknowingly apply to the affected limb, surgeons should strive for robust fixation using their preferred method of treatment delivered in an MDT environment. The application of sound biomechanical principles coupled with early recognition of perioperative complications has the potential to lead to highly successful results in "neuropathic fractures and dislocations" in patients with diabetes.

As with any manuscript, there are limitations that merit discussion. We described a method for estimating the incidence and prevalence of CNO in US patients, and compared the incidence with primary cancers, metastatic disease, and lower extremity fractures in the US population. The data presented are all estimations and calculations, in part based on epidemiologic data obtained from non-US studies. The reader should recognise that the terminology of incidence and prevalence are sometimes unspecified or unclear in the cited articles that we utilised to calculate our estimates. Additionally, the cited studies do not uniformly describe whether active or inactive CNO (in remission) were included, and consequently, these epidemiologic estimates may be somewhat biased. The epidemiologic studies cited were not uniform in how they diagnosed CNO. The diagnosis was made mostly using retrospective retrieval of ICD 9 or 10 codes from databases or disease management programs. The exception was the Metcalf study, which audited seven hospital-based specialist services during the month of April 2017.[30] This study specifically defined active Charcot disease as otherwise unexplained inflammation, detected either clinically or by magnetic resonance imaging of the foot of a person with diabetes, with or without evidence of skeletal damage. Another limitation is that our discussion regarding surgical intervention during the active phase is not based on robust medical evidence, but rather on small non-controlled studies and expert opinion.

4 | CONCLUSION

In persons with diabetes, the number of new cases of CNO per year is higher than many primary malignancies, many de novo bone metastases, and lower extremity fractures except for fractures of the forefoot, hip, and ankle. Although adequately powered comparative studies have yet to be published, intervention during the active phase of CNO has the potential to reduce the likelihood of permanent deformity. Active CNO is a disease which ranges from normal radiographs to abnormal radiographs, and once radiographic changes are noted, intra and extra-articular osseous fractures, joint subluxation, and joint dislocation are typically seen. Realignment arthrodesis during the active stage, after an initial period of offloading and swelling reduction, stabilises the foot and mitigates the acute inflammatory response to lessen osteoclastogenesis and promote healing. Consider treating active CNO like any other intra-articular fracture, dislocation, or fracture dislocation elsewhere in the skeleton. Delaying intervention until the inactive stage of resolution with associated deformity makes surgical intervention more difficult. Methods of fixation, whether internal, external, or hybrid, have greatly improved over the past half century, and greatly enhance our ability to stabilise these injuries. Preventing deformity associated with CNO will prevent foot ulcers, infection, and amputation.

Ideally, a prospective, randomized study comparing early surgery during the active stage of CNO and standardized offloading treatment should be performed to better substantiate our recommended approach. This study would likely require the inclusion of multiple experienced centres which represent the international experience of those who treat active CNO.

AUTHOR CONTRIBUTIONS

Dane K. Wukich takes responsibility for this manuscript and co-wrote it with Robert G. Frykberg and Venu Kavarthapu.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

The authors are board members of the International Association of Diabetic Foot Surgeons. Dane K. Wukich served as chair of the IWGDF Guidelines on Charcot. Additionally, Dane K. Wukich serves on the scientific advisory board of AOTI and has served as a consultant for Stryker and Orthofix and received royalties from Arthrex. Robert G. Frykberg serves on the scientific advisory board of AOTI and VK has no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

As far as data availability is concerned, this was a review article. No study data were compiled.

ORCID

Dane K. Wukich https://orcid.org/0000-0002-3637-6208
Robert G. Frykberg https://orcid.org/0000-0001-9095-303X

PEER REVIEW

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