Review

Charcot Neuro-Osteoarthropathy in Diabetes: Implications for Diabetic Foot Ulcers, Amputations, and Survival

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Abstract

Charcot neuro-osteoarthropathy (CN) is a severe and often underrecognized complication of diabetes mellitus, primarily affecting individuals with diabetic neuropathy. Its clinical course is marked by progressive joint destruction and foot deformities. This review aims to summarize current evidence regarding the role of CN in the development and recurrence of diabetic foot ulcers (DFUs), the risk of amputation, and long-term survival outcomes, as well as to highlight key mechanisms contributing to these complications. Individuals with CN exhibit a significantly higher risk of DFUs, particularly in the midfoot region, due to structural deformities and increased plantar pressure. The risk of amputation is markedly elevated in individuals with CN, especially when DFUs are present. Mortality rates in CN are substantial, with five-year survival comparable to or worse than several malignancies. The development of foot ulcers and amputations in CN results from a complex interaction of neuropathy, structural deformity and chronic inflammation. Therefore, CN is a high-risk condition associated with serious foot complications and elevated mortality. Early recognition, multidisciplinary management, and further research into its independent prognostic impact are essential to improve long-term outcomes.

Keywords

Charcot neuro-osteoarthropathy, diabetic foot ulcer, mortality, lower-extremity amputation, limb loss, peripheral neuropathy

Introduction

Charcot neuro-osteoarthropathy (CN) is a progressive, destructive complication that primarily affects individuals with diabetes mellitus (DM) and peripheral neuropathy.[1,2] It is characterized by inflammatory-mediated damage to the bones, joints, and soft tissues of the foot or ankle, often frequently resulting in significant deformity and loss of function.[1,2] Although epidemiological data are limited, CN occurs in less than 1% of individuals with DM.[3] In those with diabetic distal symmetrical polyneuropathy, however, the incidence increases substantially, reaching up to 30%.[3]

The long-term prognosis of diabetic foot complications is often poor, with mortality rates reflecting the severity of underlying disease. The five year mortality for CN, diabetic foot ulcer (DFU), minor and major amputations is 29.0, 30.5, 46.2 and 56.6%, respectively.[4] These figures are comparable to, or even exceed, those associated with several forms of cancer, including breast cancer.[4] Notably, the five-year mortality following a major amputation surpasses that of most malignancies.[4] Multiple studies have demonstrated that individuals with CN have increased risk of developing DFU,[5-10] undergoing amputations[6,8-14] and experiencing elevated mortality.[11,13,15,16] Consequently, patients with CN who also develop DFUs or require amputations may face an even higher mortality risk.

The aim of this narrative review is to explore the role of CN in the context of diabetic foot complications, with a particular focus on its association with DFUs, lower-extremity amputations (LEAs), and mortality. By synthesizing current evidence from observational studies, clinical cohorts, and meta-analyses, this review aims to clarify the clinical burden of CN, highlight its contribution to adverse foot-related

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outcomes, and identify areas where further research is needed to better inform prevention and management strategies.

Foot Ulcers in Charcot Neuro-Osteoarthropathy

CN is frequently complicated by DFUs, which may precede, coincide with, or follow the onset of structural foot deformity. Several studies have examined the frequency of foot ulceration among individuals with CN, revealing a high prevalence of coexisting or subsequent DFU in this population (Table 1).[6-10]

In one prospective study, 115 individuals with DM were followed over a period ranging from 6 to 114 months, during which 140 feet were affected by CN.[6] Among them, 43 participants (37%) developed ulcers in 53 feet (68 ulcers), with an annual ulcer incidence of 17%. In terms of timing, a DFU developed during the active phase of CN in 7 patients. Regarding ulcer location, 15 of the 68 ulcers, including two recurrent and one bilateral case in 12 patients, were localized to the midfoot region, corresponding to the rocker-bottom deformity. The remaining 53 ulcers exhibited a distribution typical of neuropathic DFUs.[6] Based on a previous study from the same institution,[5] which reported a 4% incidence of foot ulceration among people with DM, the authors concluded that individuals with CN have a fourfold increased risk of developing DFUs compared to those with DM without CN.[6] Regarding ulcer outcomes, healing was achieved in 40 out of 43 patients (93%). Sixteen of these patients (37%) required surgical intervention. Notably, all 15 ulcers located over the rocker-bottom deformity successfully healed, with surgical resection of a bony prominence required in only one case. The three non-healing cases included two patients who underwent major amputation and one patient who died.[6] Overall, these represent favorable short-term outcomes. However, given the high risk of ulcer recurrence in this population, the long-term impact of these interventions remains uncertain.

A retrospective study evaluated the outcomes of patients with CN managed with early weightbearing using offloading devices, initially a total contact cast, followed by transition to a removable CN restraint orthotic walker once fabrication was complete.[9] A total of 62 consecutive participants, accounting for 74 affected feet, were enrolled in the study and treated for CN. Of the 74 affected feet, 48 (64.9%) developed a DFU during the course of treatment.[9] Similarly, another retrospective study examined the mortality and complications after treatment of active CN.[8] A total of 173 individuals with active CN and DM were included in the analysis. Complications, including DFUs and amputations due to DFUs or DFU risk associated with CN-related deformities, were observed in 67% of cases; however, the authors did not clearly distinguish which specific complications occurred in each case.[8] Moreover, a retrospective analysis examined four major complications associated with CN: recurrent foot ulcers, foot surgery, amputation, and mortality.[10] A total of 83 individuals with CN were included in the analysis, of whom 54 were diagnosed with active CN and 29 with chronic CN. Among thems, 63 individuals (75.9%) experienced recurrent DFUs followed by foot surgery and lower-limb amputation. Overall, 28 participants (44.4%) had more than 3 episodes of recurrent DFUs. Patients with both CN and DFUs demonstrated a significantly higher risk of recurrent DFUs [OR (95% CI): 4.27 (1.38, 13.21), $P = .01$] compared to those without DFUs. DFUs were associated with a substantial risk of recurrence.

In addition to prospective and retrospective studies, a cross-sectional study analyzed 41 patients with CN.[7] During follow-up, 20 (67%) CN-affected feet developed at least one episode of ulceration, while 12 feet (40%) experienced recurrent ulcerations. Surgical management was required in 15 feet (50%), with a mean interval of 31 months (range: 0-67 months) from diagnosis to the first operative intervention.[7]

Considering the above studies, it is clear that individuals with CN are at signtificantly increased risk of developing DFUs. Although direct comparisons between people with and without CN remain limited, existing evidence consistently indicates a markedly higher incidence and recurrence of DFUs in those affected by CN. This finding is particularly noteworthy when viewed in the context of the broader population with DM; among the estimated 537 million people globally living with DM, approximately 19% to 34% are expected to develop a DFU during their lifetime.[17] In contrast, studies in individuals with CN report ulceration rates ranging from 37% to 75%, suggesting that the presence of CN more than doubles - if not triples - the risk of developing a DFU.

Notably, many of these studies do not clearly distinguish between acute and chronic stages of CN. In the acute phase, the foot is inflamed, structurally unstable, and typically managed with strict offloading of the affected limb to prevent further joint collapse and promote resolution. This aggressive offloading may temporarily reduce the risk of ulcer development. In contrast, chronic CN is characterized by permanent structural deformities, such as a rocker-bottom foot, resulting from previous bone and joint destruction. These deformities significantly alter foot biomechanics and increase plantar pressure, making the foot more susceptible to recurrent ulceration. As such, studies that do not differentiate between the two stages may underestimate the true incidence of DFUs.

Despite the growing body of literature, several important gaps remain. Future prospective studies should aim to more precisely quantify DFU incidence and recurrence in individuals with and without CN, while also evaluating differences in healing duration, treatment outcomes, and the need for

Table 1. Summary of Key Findings from Included Studies.

Author (Year)	Study Type	Population (n)	CN Effect on Ulcer	CN Effect on LEA	CN Effect on Mortality
Yammine et al (2022)	Meta-analysis	CN (2250)	N/A	16% during first hospitalization 15% during follow-up (9% major, 5% minor)	1-year: 4% 5-year: 24.5% >7 years: 16%
Gazis et al (2004)	Prospective	CN (47) DFU (47)	N/A	23.4% major (CN group) 10.6% major (DFU group)	44.7% (CN group) 34% (DFU group)
Larsen et al (2001)	Prospective	CN (115)	37% totally 17% annually	1.7% major	1 individual
Sohn et al (2009)	Retrospective cohort	CN (1050) DFU (2100) DM (2100)	N/A	N/A	28.3% (CN group) 37% (DFU group) 18.8% (DM group)
Pakarinen et al (2009)	Cross-sectional	CN (41)	67% DFUs 40% recurrent DFUs	N/A	N/A
Bandeira et al (2023)	Retrospective	CN (27) DM (87)	N/A	CN is second most common cause of LEA after infected DFU	N/A
Rahman et al (2020)	Retrospective	CN (83)	75.9% recurrent DFUs	45.8%	N/A
Jansen et al (2018)	Retrospective	CN (173)	67%		
Nilsen et al (2018)	Retrospective	CN-affected feet (74)	64.9%	14.9% major 4.1% intermediate 6.8% minor	N/A
Van Baal et al (2010)	Retrospective	CN (70) DFU (66)	N/A	N/A	18.6% (CN group) 33.3% (DFU group)
Sohn et al (2010)	Retrospective	CN (911) DFU (15 117)	59%	DFU only: 7× amputation risk versus CN only CN + DFU: 12× amputation risk	N/A

Abbreviations: CN, Charcot Neuro-Osteoarthropathy; DM, diabetes mellitus; DFU, diabetic foot ulcer; LEA, lower extremity amputation; N/A, not available.

surgical intervention. Importantly, such analyses should stratify patients by disease stage, active versus chronic CN, as these phases may differ significantly in ulcer risk, healing capacity, and response to offloading strategies or surgical correction. Clarifying these distinctions will be essential to informing preventive strategies and optimizing long-term outcomes in this high-risk population.

Amputations in Charcot Neuro-Osteoarthropathy

LEAs represent one of the most severe and life-altering complications associated with diabetic foot disease. In the context of CN, the risk of amputation is of particular concern due to the complex interplay of neuropathy, structural deformity, and ulceration. LEAs are typically classified into two categories: minor and major. Minor amputation refers to any amputation performed at or distal to the ankle joint, typically involving the removal of one or more toes, portions of the foot, or the forefoot. Major amputation is defined as any amputation performed proximal to the ankle joint, occurring either below or above the knee. This section explores the available evidence regarding the incidence and risk of both minor and major amputations in individuals with CN, highlighting key findings from retrospective studies and addressing the variability in reported outcomes.[8-14]

Sohn et al performed a retrospective study to compare the risk of LEAs among people with CN with and without ulcers and those without CN and ulcer (only DM).[12] The analysis included 911 individuals with CN and 15 117 individuals with DFUs, after excluding individuals with a prior history of LEAs. The unadjusted amputation rates were 14.7% among patients with CN and 14.5% among those

with DFUs. Over a mean follow-up period of 37 ± 20 months for the CN group and 43 ± 18 months for the DFU group, the incidence of amputations was 4.1 per 100 person-years in the CN cohort and 4.7 per 100 person-years in the DFU cohort. The Mantel-Haenszel rate ratio was 0.88, with no statistically significant difference between the groups ($P = .15$). Therefore, in this cohort, the risk of LEA among individuals with CN was comparable to that observed in individuals with DFUs, with no statistically significant difference in amputation rates during the follow-up period. Among individuals with CN, 538 individuals (59%) received treatment for foot ulceration between 2002 and 2007. Of these, 66% (354 patients) developed foot ulcers either shortly before or at the same time as the CN diagnosis, while the remaining 34% (184 patients) developed ulcers as a subsequent complication. Compared to those with CN alone, patients with foot ulcers alone had a seven-fold increased risk of amputation, and those with both CN and foot ulcers had a twelvefold increased risk among individuals aged 65 years or older.[12] Among those under 65 years of age, the corresponding risks were ninefold and thirteenfold higher, respectively. Therefore, amputation risk was lowest in patients with CN alone, higher in those with DFUs, and highest in patients with both CN and DFUs. These findings highlight that foot ulceration is the primary driver of amputation risk in patients with CN, and that the coexistence of both conditions markedly amplifies this risk.[12]

The previously cited study by Nilsen et al also examined the rate of amputation among individuals with CN.[9] Among the 74 CN-affected feet evaluated, the overall incidence of LEA was 25.7% (19 patients). This included 11 major amputations (14.9%), 3 intermediate amputations (4.1%), and 5 minor amputations (6.8%). Infection emerged as the leading cause of amputation. Notably, hindfoot involvement was associated with a significantly higher incidence of LEA compared to cases limited to the midfoot.[9] In line with these findings, the study by Rahman et al evaluated 83 individuals with CN and similarly reported a high incidence of amputation, particularly among those with recurrent DFUs.[10] Nearly half of the patients (45.8%, $n = 38$) underwent LEA, with over half of these amputations (52.6%, $n = 20$) occurring within two years of CN diagnosis. Recurrent DFUs were the most significant predictor of amputation [OR (95% CI): 8.47 (1.83-39.16), $P = .006$], followed by a history of heart disease [OR (95% CI): 5.23 (1.42-19.20), $P = .01$] and the presence of chronic CN [OR (95% CI): 3.91 (1.12-12.99), $P = .03$]. Another retrospective analysis by Gazis et al compared mortality and LEA rates in 47 individuals with CN and a matched control group ($n = 47$) with uncomplicated neuropathic ulceration.[11] Overall, 11 patients (23.4%) in the CN group underwent major LEA on the affected limb, compared to 5 patients (10.6%) in the control group; this difference did not reach statistical significance ($P > .05$).[11]

Building on the evidence that CN, with or without coexisting ulceration, increases the risk of amputation, CN has also been identified as a major contributing factor among individuals who ultimately undergo LEA. Bandeira et al categorized 114 patients with DM according to the primary cause of lower extremity amputation.[14] Among them 27 patients had a prior history of CN, while the remaining 87 underwent amputation due to other diabetes-related complications, including infected DFU, osteomyelitis, peripheral arterial disease or fractures. Notably, CN was identified as the second most common cause of amputation after infected ulceration. The data indicate that among patients with CN who eventually underwent amputation, the timing of the procedure relative to CN diagnosis varied considerably. Specifically, 47.4% of amputations occurred within the first year following the diagnosis of CN, and an equal proportion (47.4%) occurred between 1 and 5 years post-diagnosis. Only a small fraction (5.3%) underwent amputation more than 10 years after their initial CN diagnosis. The cumulative 5-year incidence of amputations due to CN was 23.7%.[14] Amputations attributed to CN were more common among men (77.8%) and White individuals (80%). The mean age of affected patients was 62 years. Most had type 2 DM (85.7%) of more than 10 years' duration (90.9%), required insulin therapy (68%) and had a history of hypertension (73.1%).[14]

Lastly, a meta-analysis which included 16 studies, some of which were analyzed in this review, and a total of 2250 participants, examined mortality and amputation rates in individuals with CN.[13] Amputation rates were assessed both during initial hospitalization and the follow-up period in patients treated for CN. During the first hospital stay, four studies encompassing 684 feet reported a 16% amputation rate (95% CI = 0.033-0.4764, I^2=97.5%). Over the follow-up period, data from ten studies (871 feet) indicated a similar overall amputation rate of 15% (95% CI = 0.067-0.258, $I^2 = 93.6\%$), including 9% major (95% CI = 0.062-0.127, $I^2 = 60\%$) and 5% minor amputations (95% CI = 0.004-0.126, $I^2 = 94.7\%$).[13]

Overall, the available evidence underscores that CN is an important contributor to LEA risk in individuals with DM, particularly when coexisting with foot ulceration. While some studies suggest that CN alone may not confer a significantly higher amputation risk compared to individuals with DFUs, it is well established that DFUs themselves markedly increase the risk of LEA. Notably, the combination of CN and DFUs substantially amplifies this risk, reflecting the additive burden of structural deformity and ulceration on limb outcomes. Retrospective analyses consistently indicate that chronic CN, recurrent DFUs, and hindfoot involvement are key predictors of major amputation. Furthermore, CN has been identified as a primary or secondary cause of LEA in cohorts of individuals with DM, often within the first few years following diagnosis. Despite these findings, heterogeneity in study designs,

inconsistent definitions of CN stages, and limited prospective data continue to hinder the precise quantification of risk. Future research should aim to clarify the temporal relationship between CN progression and amputation, stratify risk based on CN stage and anatomical involvement, and evaluate the impact of early multidisciplinary interventions on long-term limb preservation outcomes.

Mortality in Charcot Neuro-Osteoarthropathy

Several studies have examined the long-term outcomes of individuals with CN, comparing their survival rates to people with DM with and without foot ulcers.[11,13,15,16] Given that CN is strongly associated with an increased risk of foot ulceration and lower-extremity amputation, both of which are independently linked to elevated mortality,[4] there is growing interest in understanding the prognostic implications of CN itself. This section summarizes key findings from the existing literature on mortality in CN, with emphasis on the role of comorbidities, the presence of DFUs, and other contributing clinical factors.

In a retrospective cohort study, five-year mortality risk was compared across three groups: individuals with CN (n = 1050), individuals with DM and DFUs (n = 2100), and individuals with DM without DFU (n = 2100), totaling 5250 patients.[15] The three groups were matched using propensity score matching based on patient age, gender, race, marital status, DM duration, and DM control. Among the total sample, a total of 1468 individuals (28%) died, with mortality rates of 18.8% for DM alone, 28.3% for CN and 37% for DFU. Compared with individuals with CN, those with DFUs had a 35% higher risk of mortality [hazard ratio (HR): 1.35; 95% CI: 1.18-1.54], while individuals with DM without foot complications had a 23% lower risk [HR: 0.77; 95% CI: 0.66-0.90]. Stratified analyses revealed that CN was associated with an elevated risk of mortality, regardless of the presence of DFUs or other comorbidities. Additionally, when comparing CN patients without DFU to their matched controls, the mortality risk was 63% higher among those with DFUs. This difference was significantly greater than the 30% increase observed when comparing CN patients with DFUs to individuals with DFUs alone. These findings highlight the substantial contribution of DFUs to the overall mortality risk in patients with CN.[15]

Likewise, Van Baal et al performed a retrospective analysis to compare the mortality of people with active CN with a matched cohort with uninfected neuropathic foot ulcers.[16] Overall, 70 individuals with CN and 66 matched control subjects were enrolled. During follow-up, 13 patients with CN (18.6%) died after a median of 2.1 years, while 22 subjects with uninfected neuropathic foot ulcers (33.3%) died after a median of 1.3 years; survival did not significantly differ between the two groups (log-rank $P > .05$).[16] A separate analysis was also conducted in a broader cohort of 117 patients with active CN managed between 1980 and 2007.[16] The median survival in this group was 7.88 years (range 4.0-15.4 years), which was not significantly different from that of matched patients with neuropathic foot ulcers, who had a median survival of 8.43 years (range 3.4-15.8 years). When compared to normative UK population data, life expectancy was reduced by 14.4 years in the CN group and by 13.9 years in the uninfected neuropathic foot ulcers group.[16]

In the prospective study by Gazis et al, no significant difference in survival was observed between patients with CN and a control group with uncomplicated neuropathic foot ulceration.[11] A total of 21 individuals with CN (44.7%) died after a mean follow-up of 3.7 ± 2.8 years, compared to 16 individuals in the control group (34.0%) who died after a mean of 3.1 ± 2.7 years.

Lastly, the meta-analysis by Yammine et al examined mortality rates in individuals with CN.[13] Primary findings indicated that two studies involving 255 patients reported a 1-year mortality rate of 4% (95% CI: 0.018-0.065). Additionally, seven studies encompassing 1706 subjects showed a 5-year mortality rate of 24.5% (95% CI: 0.172-0.326, $I^2 = 88.5\%$), while four studies including 277 patients showed a mortality rate of 16% after more than seven years (95% CI: 0.065-0.289, $I^2 = 84.3\%$). The mortality rate increased from 4% at 1 year to 24.5% at 5 years, before decreasing to 16% beyond seven years.

In summary, current evidence suggests that individuals with CN experience a significantly elevated mortality risk compared to those with diabetes without foot complications, and in some studies, comparable than those with DFUs. Importantly, the co-occurrence of DFUs in patients with CN appears to further amplify mortality risk, underscoring the additive burden of these complications. However, comparisons across studies are limited by differences in design, patient populations, and the extent of comorbidity adjustment. Future prospective studies with standardized definitions of CN stage and ulcer status, longer follow-up periods, and stratified analyses are needed to better elucidate the independent contribution of CN to mortality. Furthermore, evaluating the impact of early detection, multidisciplinary management, and comorbidity control on survival outcomes will be essential to guide prognostically meaningful interventions in this high-risk population.

Mechanisms Leading to Ulceration and Limb Loss in Charcot Neuro-Osteoarthropathy

Distal symmetric sensorimotor polyneuropathy, autonomic neuropathy, peripheral arterial disease, and repetitive

trauma are recognized as the principal predisposing factors for the development of DFUs.[17,18] In the context of CN, ulceration and limb loss result from a complex interplay of structural, neurological, biomechanical, and vascular abnormalities.[1,19]

Prior to the elucidation of the receptor activator of nuclear factor-κB ligand (RANKL)- receptor activator of nuclear factor-κB (RANK) - osteoprotegerin (OPG) RANK-RANKL-OPG pathway in the pathogenesis of CN, two primary theories had been widely proposed to explain its development: the neurotraumatic theory and the neurovascular theory.[1] Both theories agree that neuropathy, often triggered by minor trauma, is central to the onset of CN.[19] However, the specific type of neuropathy, whether predominantly sensory, motor, or autonomic, remained a topic of ongoing debate.[19] The neurotraumatic theory suggests that repetitive microtrauma to the foot, in the setting of peripheral neuropathy which is universally present in individuals with CN, initiates a degenerative cascade that ultimately leads to joint disintegration and structural collapse.[19] The neurovascular theory proposes that autonomic neuropathy induces an abnormal increase in blood flow to the affected area.[1,19] This excessive perfusion leads to hyperemia and an imbalance between bone resorption and formation, favoring osteoclastic activity. As a result, bone density decreases, predisposing the foot to structural weakening and deformity.[1,19]

In addition, autonomic neuropathy is also a key contributor, particularly through sudomotor dysfunction, which results in reduced sweat production and dry, fissured skin.[20,21] This compromised skin barrier further predisposes individuals with CN to ulceration and secondary infection, particularly in pressure-prone regions of the foot.

Ultimately, regardless of the predominant type, neuropathy is a fundamental driver of both CN and diabetic foot ulceration, underscoring the critical role of neuropathic complications in the pathogenesis of foot outcomes.

Regarding peripheral arterial disease, it was previously hypothesized that reduced blood flow, might exert a protective effect against the development of CN. However, emerging evidence challenges this notion, demonstrating that peripheral arterial disease and CN frequently coexist rather than being mutually exclusive conditions.[22,23] A study by Meloni et al, which included 76 patients with active CN, reported that 24 participants (31.6%) had peripheral arterial disease.[22] Similarly, a larger multicenter study by Jude et al involving 736 patients with CN, found that 146 (19.8%) had peripheral arterial disease, reinforcing the association.[23] Therefore, the coexistence of peripheral arterial disease and CN is not uncommon and should not be considered a protective factor against the onset of CN. Rather than peripheral arterial disease offering protection against CN, it is more plausible that both conditions share common underlying risk factors, including DM and systemic inflammation.[24] As a result, CN patients with peripheral arterial disease may present with distinct clinical challenges, as impaired blood supply can exacerbate complications by delaying healing and increasing the risk of ulceration and amputation. These insights underscore the importance of a comprehensive vascular assessment in individuals with CN to optimize management and prevent adverse outcomes.

Moreoever, foot deformities that develop following the consolidation phase of CN are recognized as a significant risk factor for the formation of DFUs due to the high plantar pressure.[25] Keukenkamp et al conducted a cohort analysis of data obtained from a multicentre randomized controlled trial involving 20 individuals with CN and 118 matched controls without CN.[26] All participants shared similar DFU risk factors and were prescribed custom-made footwear. Over an 18-month follow-up period, participants were evaluated for barefoot and in-shoe plantar pressures during walking, adherence to prescribed footwear, and DFU recurrence. Overall, 8 of the 20 participants (40%) in CN group had a recurrent plantar ulcer within 18 months, compared to 55 of the 118 (47%) participants in the non-CN foot group ($P = .63$). Midfoot ulcers recurred significantly more in the CN foot group (4/8) than in the non-CN foot group (1/55; $P = .001$). Median barefoot peak pressures in the midfoot were significantly higher in the CN group compared to controls (756 kPa vs 146 kPa; $P < .001$), while no significant differences were observed in other regions of the foot. In-shoe midfoot pressures were also elevated in the CN group (152 kPa vs 119 kPa), although this difference did not reach statistical significance. Among the CN group, 88% (7 of 8) of recurrences occurred in the same foot as the previous ulcer, with 57% (4 of 7) recurring at the exact same anatomical site. Similarly, in the control group, 82% (45 of 55) of DFU recurrences involved the same foot, and 78% (35 of 45) recurred at the prior ulcer location. These findings underscore the critical role of midfoot structural deformities in ulcer recurrence among individuals with CN. The markedly increased midfoot plantar pressures likely offset the benefits of improved footwear adherence, highlighting the lasting impact of CN-related deformities on foot biomechanics and the persistent risk of ulceration, particularly at previously affected sites.[26]

The current understanding of CN pathogenesis centers on the RANK-RANKL-OPG signaling pathway.[1] In this model, inflammation plays an important role, with growing evidence suggesting that pro-inflammatory cytokines are key mediators of excessive bone resorption and joint destruction.[27] The inflammatory theory of CN proposes that a heightened local inflammatory response, typically triggered by minor trauma or repetitive mechanical stress in the context of diabetic peripheral neuropathy, leads to increased expression of cytokines such as

interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).[27,28] This cytokine surge activates the RANKL pathway, promoting osteoclast differentiation and accelerating bone degradation. The resulting imbalance between bone formation and resorption drives the characteristic joint instability and deformity seen in CN. Importantly, this prolonged and dysregulated inflammatory state not only perpetuates skeletal damage but also disrupts the normal phases of wound healing, particularly during the active phase of CN.[29] These disruptions may lead to delayed re-epithelialization, poor granulation tissue formation, and a greater risk of chronic, non-healing ulcers.

Conclusions

CN represents a serious complication of DM that significantly contributes to the development and recurrence of DFUs, increases the risk of LEAs, and is associated with elevated mortality, particularly when coexisting with DFUs. However, further studies are needed to better examine these associations. The development of foot ulcers and limb loss in CN results from a complex interaction of neuropathy, structural deformity, vascular insufficiency, and chronic inflammation. Elevated midfoot pressures, impaired wound healing, and persistent inflammatory activation through the RANK–RANKL–OPG pathway contribute to a high risk of ulcer recurrence and poor outcomes. Effective management requires early detection, biomechanical offloading, and close monitoring to mitigate long-term complications.

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