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RESEARCH ARTICLE

Diagnosis and treatment of active charcot neuro-osteoarthropathy in persons with diabetes mellitus: A systematic review

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Abstract

Background: There are uncertainties regarding the diagnostic criteria, optimal treatment methods, interventions, monitoring and determination of remission of Charcot neuro-osteoarthropathy (CNO) of the foot and ankle in people with diabetes mellitus (DM). The aims of this systematic review are to investigate the evidence for the diagnosis and subsequent treatment, to clarify the objective methods for determining remission and to evaluate the evidence for the prevention of re-activation in people with CNO, DM and intact skin.

Methods: We performed a systematic review based on clinical questions in the following categories: Diagnosis, Treatment, Identification of Remission and Prevention of Re-Activation in people with CNO, DM and intact skin. Included controlled studies were assessed for methodological quality and key data from all studies were extracted.

Results: We identified 37 studies for inclusion in this systematic review. Fourteen retrospective and observational studies relevant to the diagnosis of active CNO with respect to clinical examination, imaging and blood laboratory tests in patients with DM and intact skin were included. We identified 18 studies relevant to the treatment of active CNO. These studies included those focused on offloading (total contact cast, removable/non-removable knee high devices), medical treatment and surgical treatment in the setting of active CNO. Five observational studies were identified regarding the identification of remission in patients who had been treated for active CNO. We did not identify any studies that met our inclusion criteria for the prevention of re-activation in patients with DM and intact skin who had been previously treated for active CNO and were in remission.

Conclusions: There is a paucity of high-quality data on the diagnosis, treatment, and prognosis of active CNO in people with DM and intact skin. Further research is warranted to address the issues surrounding this complex disease.

KEYWORDS
charcot foot, charcot neuroarthropathy, charcot neuro-osteoarthropathy, charcot osteoarthropathy, diabetic foot, systematic review

1 | INTRODUCTION

Charcot neuro-osteoarthropathy (CNO) is a rare, but severe and sometimes disabling complication of diabetes mellitus (DM).[1] It is viewed as an inflammatory process in persons with neuropathy which results in injury to bones, joints, and soft tissues of the foot and ankle. This soft tissue and osseous injury in patients with neuropathy may result in distortion of the architecture of the foot and ankle and long-term deformity due to fractures, dislocations, and fracture-dislocations.

Neuropathy related to DM probably affects 25%–35% of patients with DM, although both higher and lower numbers have been reported in prevalence studies and these differences may be related to factors such as the population studied and measurement techniques.[2–4] To the best of our knowledge population-based studies of sufficient size and quality are lacking. Prevalence data of 0.1%–5% of patients with DM and CNO have been reported in various settings such as primary care and centres of expertise.[5] The true incidence and prevalence of CNO is unknown likely due to the absence of pain from underlying peripheral neuropathy which may delay the presentation to health care providers or may lead to misdiagnosis. With the increasing prevalence of people with DM and neuropathy, prompt diagnosis and treatment of CNO is critical.[6] If not diagnosed and treated early, continued ambulation on a neuropathic foot with CNO may lead to deformity. The presence of deformity may lead to ulceration, infection and amputation. Studies have demonstrated a six to 12 times increased risk of major amputation in patients with foot ulceration due to CNO as compared to CNO patients without ulceration.[5,7]

The understanding of the pathophysiology of CNO has improved over the past 2 decades. Some form of trauma, recognized or not recognized by the individual with peripheral neuropathy, triggers an acute inflammatory response in the foot and/or ankle. According to current insights, disproportionate release of proinflammatory and anti-inflammatory cytokines results in activation of nuclear factor-κβ (NF-κβ) via the receptor activator of nuclear factor-κβ ligand-(RANKL) pathway, stimulating osteoclastogenesis.[8,9] This inflammatory process, in combination with the ground reactive forces applied to the lower extremity while ambulating, can lead to disruption of ligaments, joint dislocations, and fracture of the foot and/or ankle.

At the current time there are no comprehensive systematic reviews regarding the diagnostic criteria, optimal treatment methods, interventions, monitoring, and identification of remission of CNO in people with diabetes mellitus and intact skin. The aims of this systematic review are threefold. First, to investigate the evidence for the diagnosis and subsequent treatment of active CNO in persons with diabetes mellitus and intact skin. Second, to clarify the objective methods for determining remission. Third, to evaluate the evidence for the prevention of re-activation of CNO patients who are no longer in the active phase. This systematic review is the basis for the development of the International Working Group on the Diabetic Foot (IWGDF) guidelines on the diagnosis and treatment of active CNO in patients with neuropathy, DM and intact skin.[10] The guideline is published in a separate document[10] and will include recommendations, the strength of recommendations, and corresponding rationale for each recommendation. This systematic review and IWGDF guidelines[10] are meant to be read in parallel.

2 | METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11,12] and was registered in the PROSPERO database for systematic reviews (CRD42022336959). Preliminary clinical questions of interest and outcomes of interest were formulated by the authors (the members of the Working Group from multiple disciplines) and were then reviewed by 15 international external experts from geographically diverse regions of the world. Based on the feedback of the external experts, the clinical questions pertaining to diagnosis and identification of remission were then formulated in the PACO format (Population, Assessment, Comparison, Outcome) and the clinical questions pertaining to treatment and prevention of re-activation were formulated in the PICO format (Population, Intervention, Comparison, Outcome) by the authors. The GRADE System was followed and is structured by the development of clinical questions in the PACO and PICO formats. These clinical questions in the PACO and PICO format were then reviewed and approved by the IWGDF Editorial Board and were categorised as the following: Diagnosis, Treatment, Identification of Remission, and Prevention of Re-Activation.

2.1 | Eligibility criteria

2.1.1 | Background and terminology

Charcot neuro-osteoarthropathy (CNO) is an inflammatory process in persons with diabetes mellitus and neuropathy which results in

injury to bones, joints, and soft tissues. We defined active CNO as the presence of a red, warm, swollen foot with osseous abnormalities on imaging in a person with DM and neuropathy. For this systematic review, only studies that included patients with active CNO and intact skin were included for the diagnosis and treatment PACO/PICOs. Studies that reported on CNO patients with a foot ulcer were excluded as this may affect diagnosis and treatment, unless the data of patients without an ulcer were reported separately or when this was unlikely to have influenced the outcomes. To be selected for the review, active CNO was considered to be present when the authors stated that the patients had Eichenholtz Stage 0, 1, or 2, or use of the terms "acute" or "active" CNO to describe study subjects, or by the use of a clinical description of the active CNO (red, warm, swollen and inflamed foot). In 1966 Sidney Eichenholtz described the clinical stages of CNO as development (Stage 1), coalescence (Stage 2), and remodelling (Stage 3) and correlated the clinical findings of each stage with radiographic findings.[13] In 1990 Stage 0 was added as a modification by Shibata and refers to the clinical findings of active CNO but without abnormalities on plain radiographs.[14]

For this systematic review, at least 80% of participants with CNO in the included studies required a diagnosis of DM and all studies had to include greater than 10 subjects.

2.1.2 | Diagnosis clinical questions/PACOs

The population of interest for the "Diagnosis" PACOs were people with active CNO and intact skin. Diagnostic studies included were those focused on foot skin temperature assessment, the presence of oedema, blood laboratory blood tests, and diagnostic imaging in the setting of active CNO.

2.1.3 | Identification of remission clinical questions/PACOs

The population of interest for the "Identification of Remission" PACOs were people with CNO and intact skin, with the absence of clinical signs of inflammation, with or without foot deformity, and plain radiographic consolidation of fractures, if present. Studies included were those focused on foot skin temperature measurement/clinical examination findings and imaging in the setting of "remission" or "resolution" of the active CNO.

2.1.4 | Treatment clinical questions/PICOs

The population of interest for the "Treatment" PICOs were people with active CNO and intact skin. However, studies including people with ulceration but no infection were included for the offloading and medical treatment PICOs only if it was deemed by the authors that the presence of ulceration would not impact intervention. Intervention studies included those focused on offloading (total contact cast, removable/non-removable knee high), medical treatment (bisphosphonates, calcitonin, denosumab, parathyroid hormone, methylprednisolone, or vitamin D) and surgical intervention in the setting of active CNO were included.

2.1.5 | Prevention of re-activation clinical questions/PICOs

The population of interest for the "Prevention" PACO were people with CNO who had a previous diagnosis of active CNO but with resolution of symptoms demonstrated by clinical examination findings and imaging.

2.1.6 | Outcomes

Outcomes of interest for the "Treatment" Clinical Questions/PICOs included a shorter time to remission and prevention of the development of complications (prevention of deformity development, prevention of deformity progression) and adverse effects of treatment (e.g. development of pressure ulcers).

2.1.7 | Eligible study designs

Systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), cohort studies, case control studies, interrupted time series, non-controlled prospective or retrospective studies, cross-sectional studies, and case series were all eligible for inclusion. Case studies, commentaries, and published conference abstracts were not included.

2.2 | Search strategy

2.2.1 | Validation set

A validation set of 33 publications was created[5,7,15–45] that included key studies on the topic of CNO. The search strings were validated by using this set. Each publication in the validation set was identified before the search for the systematic review was performed.

2.2.2 | Search

The search was performed on 3 March 2022 and included studies in any language up to the date of the search. The search string was devised with the assistance of a university librarian who also performed the search. The following databases were searched: Cochrane CENTRAL, Ovid MEDLINE, Ovid MEDLINE InProcess and EPub and Ovid Embase. The search strings are shown in

Appendix 1. The search was again performed on 14 November 2022, to identify any additional eligible studies published after 3 March 2022.

2.2.3 | Eligibility assessment

After the literature search was performed, two authors performed the screening of the titles and abstracts for eligibility based on the pre-determined inclusion and exclusion criteria which were based on the PACOs and PICOs. Disagreements were discussed between the authors until consensus was reached. The studies deemed eligible were included for the full text review phase.

Two authors then independently assessed the full text of each eligible study. The full text was reviewed for the same inclusion and exclusion criteria. Any disagreements regarding the inclusion of a study were discussed by members of the Working Group until agreement was reached. The online systematic review tool Rayyan (https://www.rayyan.ai) was used for tracking of the studies.

2.2.4 | Qualitative assessments

All studies included were assessed for study design, methodological quality, the level of evidence and key data.

2.2.5 | Study design assessment

The authors reviewing the studies included jointly classified the study design using the SIGN algorithm (http://www.sign.ac.uk/pdf/study-design.pdf). Studies classified as being a controlled study design (RCT, controlled cohort, case control studies) were assessed for methodological quality and key data were extracted. Studies classified as being a non-controlled design were narratively described and key data from these studies were extracted if no controlled studies were identified that addressed the clinical question or if the non-controlled studies added relevant evidence.

2.2.6 | Risk of bias/methodological quality assessment

The risk of bias/methodological quality was assessed independently by two authors for the included studies treated as a controlled study design. For controlled studies, this was performed using one of two Dutch Cochrane Centre quality assessment tools: a 10-item tool for RCTs or a 10-item tool for cohort studies (www.cochrane.nl). Also, for all controlled studies, the 21-item IWGDF quality assessment tool on reporting standards for diabetic foot studies was used.[46] All non-controlled studies were automatically deemed as Level 3 evidence and not assessed for risk of bias. Disagreements were discussed until a consensus was reached.

2.2.7 | Level of evidence assessment

For each controlled study, two authors jointly used the study design and methodological quality assessment to determine the level of evidence. Level 1 evidence referred to meta-analyses, systematic reviews, or RCTs. Level 2 evidence referred to NRCTs, cohort, case control, or interrupted time series studies. The risk of bias was then scored using the total methodological quality assessment score obtained from the respective SIGN or Dutch Cochrane Centre tools as follows: ++ (very low risk of bias) for any meta-analyses scoring greater than or equal to 10/12, or any controlled study scoring greater than or equal to 8/10; + (low risk of bias) for any meta-analyses scoring a 7 to 9/12, or any controlled study scoring 6 to 7/10; and - (high risk of bias) for any meta-analyses scoring less than or equal to 6/12, or any controlled study scoring less than or equal to 5/10. Equal weighting was applied to each item in the SIGN or Dutch Cochrane. As previously stated, all non-controlled studies were automatically deemed as Level 3 evidence and not assessed for risk of bias.

2.2.8 | Data extraction assessment

Key data were extracted for all studies (see Appendix 2A–2C). This is summarised in evidence tables. One author extracted the data and a second author checked for accuracy. All authors reviewed and discussed the evidence tables. Data extracted included study design, population, diagnostic tools/modalities, interventions, reported results/outcomes, and key findings.

2.2.9 | Evidence statements

For each PACO and PICO, a summary of the evidence from the included studies was drafted by two authors and then presented to the Working Group for review and discussion. The summary of the evidence presented was based on the studies included for each PACO/PICO. The Working Group then formulated evidence statements based on the gathered and presented evidence. If no evidence was identified for a PACO or PICO then an evidence statement was not formulated. The authors then rated the quality of evidence (QoE) for each statement as "low," "moderate," or "high".[47–49] The rating of the QoE for our PICOs was based on the confidence we had regard to what extent the true effect lies close to that of the estimate of the effect based on our literature search.[49] For the PACOs, we used the same approach for the rating of diagnostic accuracy.

3 | RESULTS

Our search identified a total of 3349 studies. After the removal of duplicates, 2315 studies were included in the title/abstract screening phase. One hundred and two studies were included for full text

review (this total included one additional study that was identified outside of the database search via reference checking). After full text review, 37 studies were identified for inclusion in this systematic review (see Prisma Flow Chart Figure 1). In this section, the clinical questions of interest with their corresponding PACO(s)/PICO(s) format, a summary of evidence, evidence statement, quality of evidence rating, and references are presented.

3.1 | Diagnosis

Clinical Question: In a person with diabetes mellitus and intact skin, in whom active Charcot neuro-osteoarthropathy (CNO) is considered, what is the accuracy of clinical findings to diagnose active CNO?

PACO: In a person with diabetes mellitus and intact skin in whom active CNO is considered, what is the accuracy of clinical findings using imaging as a comparator to predict active CNO?

Summary of the Evidence: We identified one retrospective case series that evaluated foot skin temperature at the time of diagnosis in patients with active CNO and intact skin using dermal infrared thermometry.[50] Twenty-one patients with DM and active CNO were compared to 78 patients with DM and asymptomatic sensory neuropathy. A group of patients with diabetes related foot ulceration was also reviewed in this study but were not included in this systematic review and will not be discussed as the presence of ulceration was an exclusion criterion for this PACO. Foot skin temperature measurements were made at the anatomic site of pathology using a portable handheld infra-red skin temperature probe at the time of the initial diagnosis and at each subsequent visit. Temperature measurements were made after subjects rested for 15 min in the examination room. The ambient air was controlled at 70 ± 0.2˚ Fahrenheit (21.1 ± 0.1˚ Celsius). The authors identified a significant difference at the time of diagnosis of the skin temperature between the affected active CNO foot and the contralateral non-affected foot (8.3˚F or 4.6˚C). No difference in skin temperature was identified between sites measured on both feet of each patient in the asymptomatic sensory neuropathy group. Based on this study, elevated foot skin temperatures measured using a hand-held infrared device seems compatible with the diagnosis of active CNO, but we could not identify any study that reported on the accuracy or reliability of clinical findings, including measurement of foot temperature or left-right foot temperature difference.

Evidence Statement: We identified no evidence on the diagnostic accuracy of temperature difference between feet in patients with suspected active Charcot neuro-osteoarthropathy.

Quality of Evidence (QoE): Low: based on one retrospective case series.

References: Armstrong et al. 1997[50]

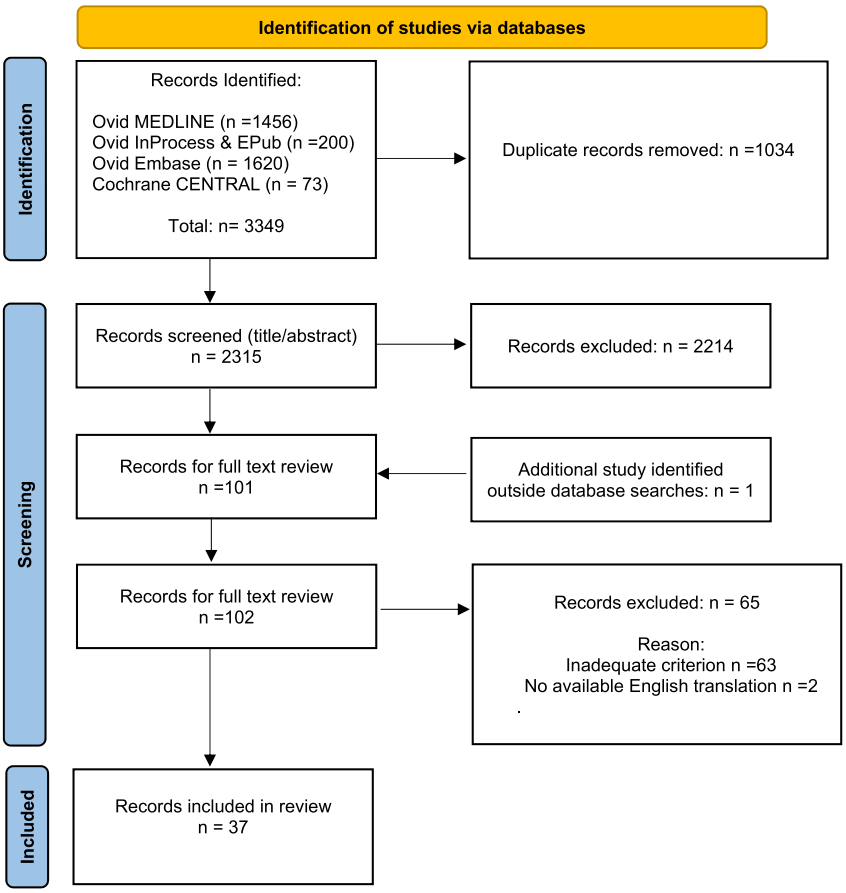

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Clinical Question: Which imaging modalities have sufficient accuracy to render the diagnosis of active Charcot neuro-osteoarthropathy (CNO) more likely in a person with diabetes mellitus and intact skin in whom the diagnosis of active CNO is considered?

PACO: Which imaging modalities have sufficient accuracy to render the diagnosis of active CNO more likely in a person with diabetes mellitus in whom the diagnosis of active CNO is considered?

Summary of the Evidence: We identified four studies that reviewed MRI findings, all from the same centre[51–54] and three studies that evaluated findings on nuclear imaging[24,55,56] in patients with suspected active CNO and intact skin at the time of diagnosis. The MRI studies included were a retrospective review,[51] a retrospective observational study,[52] a retrospective case series,[53] and a retrospective observational cohort study.[54] The nuclear imaging studies included two retrospective cohort reviews[24,55] and one before-after interrupted time series.[56] All studies included for this PACO were observational studies and therefore no risk of bias assessment was made.

In Chantelau's 2005 retrospective study, 24 patients with active CNO were evaluated after referral to the author's centre.[51] Eleven had been referred before osseous abnormalities were detected on radiographs (early treatment group) and 13 were referred after osseous abnormalities were detected on radiographs (delayed treatment group). All patients were immediately immobilised in a TCC upon presentation. Of the 11 patients referred to early (abnormalities identified on advanced imaging, referred before changes detected on radiographs) only 1 developed fracture/deformity compared to 12 out of 13 of the patients in the delayed referral group (no advanced imaging, referred after fractures detected on repeat radiographs), who developed fracture/deformity ($P < 0.001$). The author concluded that advanced imaging with MRI led to prompt treatment and improved outcomes. Chantelau and Poll's 2006 retrospective observational study[52] included 18 feet with active CNO and intact skin; 7 feet in Eichenholtz Stage 0, 11 in Eichenholtz Stage 1, and 3 feet in Eichenholtz Stage 2. The authors also evaluated 5 feet in Eichenholtz Stage 3 but for purposes of this review, these will not be discussed. All patients underwent MRI. All MRIs performed detected osseous abnormality in patients with active CNO, demonstrating high sensitivity. A 2007 retrospective case series[53] analysed 12 patients with suspected active CNO, intact skin, and normal radiographs in whom MRI was performed to confirm or exclude active CNO. Bone abnormalities were present on all MRIs. A retrospective observational cohort study[54] examined 27 cases of Stage 0 and 44 cases of Stage 1 active CNO. All cases of active CNO and intact skin in both Stage 0 and Stage 1 were diagnosed by MRI. Prompt MRI led to earlier diagnosis and ultimately less deformity development. Nineteen (70%) of the people in Stage 0 healed without deformity and 14 (32%) of the people in Stage 1 healed without deformity during the follow-up period.

Nuclear imaging: Two retrospective cohort reviews[24,55] and one before-after interrupted time series[56] were identified in our systematic review. Ahluwalia et al.'s retrospective cohort review of 46 patients demonstrated abnormality on a three-phase bone scintigraphy with high resolution Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT) in all patients with suspected active Charcot (all Eichenholtz Stage 0), intact skin and normal radiographs.[24] They described the "distinct bone pathology" of the patients and classified them into three groups based on the imaging findings. All patients were treated with below knee casting and in the 24 month follow-up period only 4 patients progressed to Eichenholtz Stage 1. In Fosbol's retrospective cohort study 148 patients with suspected active CNO were included and the diagnosis of active Charcot was made in 90 patients (61%). In all patients 99 mTc-hydroxymethylene diphosphate three-phase bone scintigraphy was performed.[55] The sensitivity, specificity and accuracy of three-phase bone scintigraphy without/with quantitative analysis were 89%/88%, 58%/62% and 77%/78%, respectively, demonstrating high sensitivity but limited specificity.[55] Ruotolo et al. investigated the usefulness of 18F-FDG PET/CT scanning in 25 patients with suspected active CNO demonstrating increased uptake in all patients.[56]

Evidence Statement A. Patients with clinical signs of active CNO and intact skin, confirmed by MRI, can have normal radiographs. However, sensitivity and specificity of radiographs to diagnose or exclude active CNO have not been reported.

QoE: Low

References: Chantelau 2005,[51] Chantelau and Poll 2006,[52] Chantelau et al. 2007,[53] Chantelau and Richter 2013,[54] Ruotolo et al. 2013.[56]

Evidence Statement B. Evidence suggests that MRI has sufficient diagnostic accuracy to render the diagnosis of active CNO (in patients with intact skin) likely and to exclude it.

QoE: Low

References: Chantelau 2005,[51] Chantelau and Poll 2006,[52] Chantelau et al. 200 7,[53] Chantelau and Richter 2013.[54]

Evidence Statement C. Nuclear imaging can detect active CNO with high sensitivity but low specificity.

QoE: Low.

References: Ahluwalia et al. 2020,[24] Fosbol et al. 2017,[55] Ruotolo et al. 2013.[56]

Clinical Question: Which blood tests have sufficient accuracy to make the diagnosis of active Charcot neuro-osteoarthropathy more likely in a person with diabetes mellitus and intact skin?

PACO: Which blood tests have sufficient accuracy to render the diagnosis of active CNO more likely in a person with diabetes mellitus using imaging as a comparator in whom the diagnosis of active CNO is being considered?

Summary of the Evidence: We identified five observational studies where erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or alkaline phosphatase was measured at baseline/initial presentation in patients with active CNO and intact skin.[40,57–60] Four studies measured CRP,[40,58–60] two studies measured ESR,[40,58] and three studies measured alkaline phosphatase at baseline.[40,57,59] All studies were of low quality and at high risk of bias.

A retrospective case series of 36 patients with active CNO and intact skin by Petrova et al.[59] reported measurements of CRP, ESR, and alkaline phosphatase at the time of diagnosis of active CNO. Result data were presented as median (25th-75th percentile) values. The median CRP was 5.8 mg/L[5–11] and was ≤5 mg/L in 47.2% of the patients at presentation. The median ESR was 21 mm/h.[13–36] Median alkaline phosphatase (standard assay 30–130 IU/L) at presentation was 105 U/L (76–136). Baseline data for the measurement of high sensitivity CRP and serum bone-specific alkaline phosphatase was extracted from Petrova et al.'s 2015 prospective, cross-sectional study of 35 patients with active CNO and intact skin.[40] Various serum inflammatory and bone turnover markers of the 35 patients with active CNO and intact skin were measured and compared to subjects in two other groups; patients with DM only and no CNO ($n = 34$) and healthy control subjects ($n = 12$). For the purpose of this systematic review/PACO, only CRP and serum bone-specific alkaline phosphatase measurement data at the time of presentation were extracted from this study. Data were reported in median (25th-75th percentile) values. Patients with active CNO had significantly higher CRP compared to both patients with DM but without active CNO ($p = 0.045$) and compared to the healthy controls ($p = 0.005$). In patients with active CNO the median CRP was 5.4 (1.8–19.9) mg/L and in the DM control group 3.7 (1.1–5.7) mg/L. In the healthy control group, the median CRP was 0.8 (0.4–2.1) mg/L. In patients with active CNO, the median serum bone specific alkaline phosphatase was 16.4 (11.7–26.2) μg/L and in the diabetes mellitus group 13.6 (11.1–17.5) μg/L. The healthy control group median was 10.1 (8.0–11.9) μg/L. Also, serum bone specific alkaline phosphatase in active CNO patients was not significantly elevated compared to patients with DM without active CNO ($p = 0.158$) but were higher compared to healthy controls ($p = 0.006$).

Data of CRP and ESR at initial presentation of active CNO patients with intact skin were extracted from Folestad et al.'s observational, prospective study that primarily focused on the role of cytokines in these patients.[58] Data extracted from 26 patients with active CNO were compared to data from 20 patients with DM-related neuropathy and 20 healthy controls. Mean CRP was elevated in patients with active CNO compared to both the patients with DM-related neuropathy ($p = 0.044$) and to the healthy controls ($p = 0.012$). Also mean ESR was elevated in patients with active CNO compared to both the patients with diabetic neuropathy ($p = 0.001$) and the healthy controls ($p < 0.001$). Baseline CRP data were extracted from Schara et al.'s observational study of 35 patients with active CNO.[60] Mean CRP in was 19 ± 45 mg/L. It should be noted that the description of patients included in their methods section states "all presented with a unilateral red, hot (>2°C difference from the contra-lateral foot), swollen foot in the presence of neuropathy and a normal peripheral circulation," however whether or not the skin was intact was not specifically described.[60]

Gough et al. performed an observational, cross-sectional study evaluating bone turnover markers in 16 patients with active CNO compared to 10 patients with inactive CNO, 10 diabetes mellitus control patients and 10 healthy controls.[57] Mean alkaline phosphatase in patients with active CNO was 78.7 ± 1.4 mg/L, in patients with inactive CNO was 92.5 ± 1.4 IU/L, in the diabetes mellitus controls, it was 66.7 ± 1.5 IU/L, and in the healthy controls it was 50.8 ± 1.2 IU/L (standard assay 30–120 IU/L). Hingsammer et al performed a retrospective review of 42 patients with CNO of which 29 were Eichenholtz Stage 0 or 1.[61] These patients had significant elevation of CRP and ESR ($p = 0.01$, $p = 0.02$) compared to the 13 patients classified as Eichenholtz Stage 2 and 3.[61] It should be noted that for this study, key exclusion criteria were surgery on the affected foot within a 12 month period prior to referral and presence of wound or ulcer. Only patients with intact skin were analysed, thus we included this study in our review.

Evidence Statement: We identified no evidence regarding the diagnostic accuracy of ESR, CRP, or (bone-specific) alkaline phosphatase when using imaging as a comparator in patients with diabetes mellitus, intact skin, and suspected active CNO. However, the available data do suggest that these laboratory tests have little added value in diagnosing or excluding active CNO.

QoE: Low

References: Gough et al. 1997,[57] Hingsammer et al. 2016,[61] Folestad et al. 2015 (baseline data),[58] Petrova et al. 2007,[59] Petrova et al. 2015 (baseline data),[40] Schara et al. 2017.[60]

3.2 | Identification of remission

Clinical Question: Which clinical examinations and imaging techniques can be used to ascertain the remission of Charcot neuro-osteoarthropathy (CNO) in a person with diabetes mellitus and intact skin who has been treated for the disease?

PACO 1: In a person with diabetes mellitus and CNO who have been treated, does normal temperature difference have sufficient accuracy to ascertain remission as defined by imaging?

Summary of the Evidence: We identified five studies that evaluated different monitoring techniques as methods for defining remission after treatment of active CNO.[62–66] These were observational studies, at high risk of bias. Two studies reported the predictive value using infrared thermometry to monitor and identify remission based on clinical findings.[62,64] The remaining studies used MRI to identify remission and also reported foot skin temperature measurement.[63,65,66] None of these studies reported the sensitivity or specificity of using foot skin temperature to identify remission.

Armstrong and Lavery's observational study measured foot skin temperature in 39 subjects with active CNO during the course of treatment and at resolution of symptoms to monitor healing.[62] Forty-four percent of patients had an active ulceration (no underlying osteomyelitis) at the time of presentation. Foot skin temperature was obtained using a portable infrared thermometric probe. Temperature was measured after subjects rested in the examination room for 15 min. The ambient air temperature was controlled between 70.0 °F (21.1°C). The contralateral foot was used as a control and the skin temperatures on the affected foot were compared to the corresponding sites on the contralateral control foot. The difference

between the two corresponding sites was recorded as the skin temperature gradient. The subjects were followed for an average of 22.6 ± 7.1 months (range 12–37 months) after return to shoes. The authors reported no significant difference in skin temperature gradients on initial presentation between ulcerated and nonulcerated subjects. Mean skin temperature difference at the time of active CNO presentation was 8.8 ± 2.3˚F (range 5.1 to 14.7˚F) (Celsius 4.9 ± 1.3 C˚, range 2.8 to 8.2˚C). Elevated foot skin temperature directly correlated with the radiographic anatomic location of active CNO in 92% of cases. A steady and gradual decrease in temperature gradient was observed during treatment as clinical symptoms resolved. The skin temperature gradient was "near zero" after transition to prescription shoes. The authors reported that a "generally small" skin temperature gradient between the affected CNO and control foot was present during the follow-up period and that this skin temperature gradient correlated to the site of maximum CNO deformity in 72% of cases during the follow-up period. The authors reported no "recurrences of Charcot fractures" during the follow-up period that averaged 2 years. The authors attribute the low rate of "re-injury" to "aggressive early intervention when subjects demonstrated an increase in more than 4˚F (or 2.2˚C) compared to the opposite foot." The 4˚F (2.2˚C) cut-off point was determined by the author's observation that temperature gradients of 3 or 4 ˚F (1.7 or 2.2˚C) can be difficult to detect with manual palpation.

Moura-Neto et al's observational study of 28 persons with active CNO used foot skin temperature measurement to determine the timing of immobilisation cessation.[64] The presence of ulceration was not specified. All patients were immobilised in a Charcot Restraint Orthotic Walker (CROW) and had monthly follow-up visits for 1 year. Radiographs were obtained at each follow-up visit. Foot skin temperature was measured on the affected foot and contralateral foot using an infrared skin thermometer. Immobilisation was discontinued when the temperature difference was less than 2˚C (3.6˚F). Patients were followed for a year after the discontinuation of immobilisation. Mean time to consolidation was 6.6 months (range 3–12 months) with a one-year consolidation rate of 89.3%. Relapse was defined as "a new elevation of temperature difference to greater than 2˚C." Of the 25 patients who consolidated, there were none who relapsed. The authors concluded that skin temperature difference of below 2˚C was an effective parameter to allow for the discontinuation of immobilisation.

Zampa et al. analysed in a cohort study the usefulness of MRI to monitor treatment and healing times in 40 subjects with active CNO.[63] They performed dynamic MRI scans, with gadolinium contrast medium every 3 months. Foot skin temperature difference measurement was also recorded. The authors reported a 90% agreement between the clinical findings and MRI findings. However, in 23% of participants healing based on clinical ground was 3–6 months prior to healing as defined by MRI. Mean healing time was 6.8 ± 2.3 months based on clinical examination (median 6 months) and 8.3 ± 2.9 months on MRI (median 8 months; $p < 0.0001$). The authors did not analyse the results of skin temperature separately.

Chantelau et al.'s 2018 observational, retrospective uncontrolled cohort study of subjects treated for active CNO used clinical findings and MRI to determine the timing when treatment should be stopped.[65] Patients who underwent treatment of active CNO and who had a baseline and follow-up MRI for review were included. Forty-five scans in 37 patients were reviewed. Oedema-equivalent signal changes (EESC) on MRI were studied. Oedema-equivalent signal changes were found to decrease on MRI in response to offloading (Decreasing EESC documented in 69% of follow up studies). Schlossbauer et al.'s 2018 study of patients with active CNO compared contrast MRI to clinical parameters of inflammation, pain, erythema, oedema, and temperature.[66] They did not report the details on the protocol used for the assessment of foot temperature.

Evidence Statement A: There is limited evidence that there is a relationship between a reduction in foot skin temperature and an improvement in foot imaging over time during treatment with offloading for active CNO.

Evidence Statement B: As data on diagnostic accuracy to determine remission are lacking in people with active CNO and treated with offloading, there is insufficient evidence to use temperature difference to ascertain remission as defined by imaging.

Quality of Evidence (QoE): Low

References: Schlossbauer et al. 2008,[66] Moura Neto et al. 2012[(64)], Zampa et al. 2011,[63] Chantelau et al. 2018,[65] Armstrong and Lavery 1997.[62]

PACO 2: In a person with diabetes mellitus and CNO who have been treated, does the resolution of oedema have sufficient accuracy to ascertain apparent remission as defined by imaging?

Summary of the Evidence: We identified two studies which compared objective assessment of soft tissue oedema to radiological findings.[63,66] We identified one study that evaluated soft tissue oedema subjectively.[65] All were observational studies, at high risk of bias and were also used for the above PACO 1.

In addition to foot skin temperature measurement, Zampa et al objectively assessed the ankle and midfoot circumference in conjunction with dynamic MRI (D- MRI) to monitor patients with active CNO and at resolution.[63] Baseline contrast medium uptake on D- MRI was not significantly related to difference in ankle or midfoot circumference (difference between the affected and unaffected foot). Schlossbauer's study used a comparison of the measurement of midfoot and ankle circumference, between the affected and unaffected limb combined with foot temperature to determine clinical remission.[66] This study reported a shorter time to remission identified by clinical assessment (6.8 ± 2.3 months), compared to MRI (8.3 ± 2.8 months). Chantelau et al's 2018 study evaluated oedema-equivalent signal-changes (EESC) on MRI in patients with active CNO.[65] According to the authors, clinical findings were not objectively measured but were "rated semi-quantitatively" and "by inspection." There was no correlation between clinical assessment in those with regression of EESC on follow-up MRI (69% of studies). A narrative description of the subjective soft tissue oedema assessment was reported alongside the EESC for cases of temporary increasing, migrating or stagnating EESC.[65]

Evidence Statement A: There is limited evidence that there is a relationship between a reduction in soft tissue oedema and an improvement in foot imaging over time during treatment with offloading for active CNO.

Evidence Statement B: In people with active CNO treated with offloading there is insufficient evidence to use a reduction in soft tissue oedema to ascertain remission as defined by imaging.

Quality of Evidence (QoE): Low

References: Zampa et al. 2011,[63] Schlossbauer et al. 2008,[66] Chantelau 2018[65]

3.3 | Treatment

Clinical Question: Which type of offloading device should be advised to a person with diabetes mellitus and active Charcot neuro-osteoarthropathy (CNO) with intact skin and should this be accompanied by non-weight bearing advice?

PICO 1: In a person with diabetes mellitus and active CNO, is any offloading device superior to no offloading device to achieve a shorter time to apparent remission and to prevent the development of complications?

Summary of the Evidence: Our systematic review identified three studies pertinent to this PICO, two retrospective case series[51,67] and a retrospective case control study.[68] Griffiths and Kaminski's retrospective case series[67] evaluated 27 patients with active CNO (defined as Eichenholtz stage 0 or 1).[67] Their aim was to evaluate the duration of treatment with total contact casting as well as any patient-related factors that affected the treatment duration. Patients were treated with TCC for active CNO and were followed until healing in the cast was achieved and beyond, to include post cast treatment, with a median follow-up 11.9 (IQR 2.8–14.6) months. Median time to resolution was 4.3 (IQR 2.7 to 7.8) months. No clinical characteristic (such as impaired kidney function or congestive heart failure) was associated with a time to resolution, except presence of pre-existing osteoarthritis which was associated with longer treatment duration, >4 months: $n = 10$ versus < 4 months $n = 3$ ($p < 0.05$).

Kimmerle and Chantelau's case-control retrospective observational study of 34 patients with active CNO evaluated the impact of unrestrained weight bearing prior to active CNO diagnosis in patients with diabetes-related neuropathy after a non-fracture injury.[68] Patients were excluded if they had a history of a previous CNO diagnosis, ulceration, DVT, or cellulitis. Patients presented initially with clinical signs of active CNO. Patients were categorised into three groups depending on the degree of their deformity; Group A consisted of 16 patients with no deformity, Group B included 6 patients with "mild" deformity, and Group C included 12 patients with "severe" deformity. All patients presented with diabetes-related neuropathy and a red, hot, swollen, foot, with only mild or absent pain, foot radiographs or MRI compatible with bone or joint injury and swelling for less than 2 weeks. The mean duration of treatment: Group A: 15 weeks, Group B: 16.7 weeks, and Group C: 25 weeks. Group A duration of treatment was significantly shorter than Group C ($p < 0.05$). Mean BMI and weight bearing intensity was also calculated for each group. The method used for calculating weight bearing intensity was body weight multiplied by weeks of unprotected ambulation prior to diagnosis. This did not include weight bearing intensity once TCC was applied. At the end of treatment, 2 patients in Group A, 6 in group B and 12 in group C respectively developed deformity. The authors concluded that unrestrained weightbearing (>400 kg/week, "the equivalent of 8 weeks of normal walking by a person of 50 kg body weight") prior to treatment with TCC was associated with the development of foot deformity.

Chantelau's 2005 retrospective case series assessed the clinical course of 24 patients with active CNO who had normal radiographs after the onset of symptoms.[51] Eleven patients were referred "early" (incipient CNO foot, case group) and 13 were referred "late" (overt CNO control group). Upon initial examination, all patients in both groups were treated with total contact casting until healing. Healing was defined as the absence of the clinical signs of inflammation and bone remodelling on radiographs (Eichenholtz Stage 3). The mean time from the onset of symptoms until the application of the TCC was 1.0 (range 0.5–5) months in the incipient CNO group versus 3 (range 1–12) months in the overt CNO control group ($p > 0.05$). The time from the start of treatment to healing was 3^{2-9} months in the incipient CNO group, versus 5.5^{2-12} months in the overt CNO control group ($p > 0.05$). In the incipient CNO group, 1/11 developed "gross foot deformity" compared to 12/13 patients in the overt CNO control group ($p < 0.001$).

Evidence Statement A: There is conflicting evidence on the association of the duration of signs and symptoms of active CNO before start of TCC treatment and subsequent duration of TCC treatment.

QoE: Low

References: Griffiths and Kaminski 2021,[67] Kimerle & Chantelau 2007,[68] Chantelau 2005.[51]

Evidence Statement B: When treatment of active CNO with a TCC is started before a fracture can be observed on plain radiographs, the incidence of severe deformity may be lower compared to patients who already have fractures on plain radiographs, but the duration of casting treatment does not seem to be markedly different between the two groups.

QoE: Low

References: Chantelau 2005,[51] Kimerle & Chantelau 2007.[68]

Evidence Statement C: There is indirect evidence that the immobilisation of the affected foot in active CNO with an offloading device may prevent the development of deformity.

QoE: Low

References: Chantelau 2005,[51] Kimerle & Chantelau 2007.[68]

Evidence Statement D: Early immobilisation of the affected foot with active CNO in an offloading device may prevent the development of deformity.

QoE: Low

References: Chantelau 2005,[51] Kimerle & Chantelau 2007.[68]

PICO 2: In a person with diabetes mellitus and active CNO, is a non-removable device superior to a removable device to achieve a shorter time to apparent remission and to prevent complications?

Summary of the Evidence: We identified nine studies that met the inclusion criteria for this PICO. Three retrospective case series,[51,67,69] five retrospective non-comparative case series,[70–74] and one case control study.[68]

In Chantelau's 2005 retrospective case series of 24 patients with active CNO, all patients were treated with a bivalved total contact cast (TCC) but it was not clear if this was removable or non-removable.[51] In Griffiths and Kaminski's retrospective case series of 27 patients, all patients were treated with a non-removable TCC.[67] The details of the Griffith and Kaminki and Chantelau 2005 studies were discussed in the previous section for PICO 6.1. In Griffith and Kaminski's study, TCC related complications developed in 59.3% of the participants.

In Fejfarova et al's study of 74 patients, all were treated with a removable TCC.[69] Patients were divided into three groups; Group A: Nonhealing neuropathic ulcers ($N = 27$), non-CNO. Group B: Diabetes mellitus, peripheral neuropathy and active CNO: hot, swollen foot with/without redness, with increased temperature of 2°C or more compared to the contralateral foot, positive x-ray and bone scan ($N = 35$), and Group C: Neuropathic fractures with radiographic location not typical for CNO with absent swelling and absent redness ($N = 12$). Of the 35 patients with active CNO (group B), 57% had broken their TCC, 30% developed a new ulcer, 9% had local progression, and 3% reported joint pain during their course of treatment. Christensen et al. in 2012 reviewed the duration of offloading and its association with recurrence in a group of 56 people with active CNO who were treated with a removable air cast walker that included an individually moulded insole and crutches.[70] Recurrence was defined as new swelling and skin temperature difference of more than 2°C (3.6˚F) in the same foot occurring after a stable interval of at least 1 month after full weight bearing. The time to remission for all participants was 141 (±21) days. Seven (12%) developed recurrence after initial casting treatment. They found no relationship between the duration of initial offloading treatment and recurrence. Adverse events were not reported. De Souza's retrospective non-comparative series investigated in 27 patients (34 feet) with active CNO and the outcomes of permitted weight bearing in a non-removable TCC.[71] The mean treatment time in TCC was 14 weeks (4–20 range). No negative effects of weight bearing (such as ulcer development or "deterioration of the osseous architecture") in a TCC were observed in 33/34 feet.

Fabrin et al's retrospective non-comparative case series evaluated the long-term outcomes of 115 patients (140 feet) treated for active CNO.[72] Three patients had "excessive swelling" and were initially treated with a few days of immobilisation in bed or in a wheelchair (sometimes in the hospital) and non-removable TCC, in order to reduce the oedema ($n = 3$), followed by the "weight off regimen". The "weight off regimen" involved two crutches and foot protection involving therapeutic footwear and orthotics with a rigid bottom and pedal arch support which was started initially in 112 patients. Time to remission was not reported. Forty-seven percent experienced foot ulceration and/or CNO recurrence. One patient underwent below knee amputation due to an ulceration caused by a cast during treatment.

Parisi et al.'s retrospective non-comparative case series evaluated 22 patients with active CNO (without history of ulcer or osteomyelitis) treated with a walker boot and full weightbearing.[73] Radiographs and temperature measurements were used for monitoring. Mean treatment time was 18 weeks. Radiographs at the end of treatment showed a relative increase in mean measured radiographic angles (such as talar-first metatarsal angle) ($p > 0.05$). No ulcerations or infections developed during the treatment period. Sinacore's 1998 study was a retrospective non-comparative case series that evaluated healing time by foot location in 30 participants with active CNO.[74] Treatment consisted of TCC with initial 24 h of non-weight bearing followed by partial weight bearing with assistive devices (e.g., bilateral crutches) and instructions to limit regular weight bearing activities (30% had forefoot or mid foot plantar ulcers). Compared to forefoot, active CNO in the ankle, hindfoot and midfoot took longer to heal with TCC (forefoot 55 ± 17 days, midfoot 96 ± 11 days, hindfoot 97 ± 16 days, ankle 83 ± 22 days). Twenty-eight percent of patients complied with the partial weight bearing instructions. Patients who did not comply took an average of 34 days longer to achieve healing ($p < 0.05$). Adverse events related to treatment were not reported.

As already discussed in this review, Kimmerle and Chantelau's 2007 study treated 34 patients with a removable fibreglass TCC and demonstrated that unrestrained weightbearing (>400 kg/week) prior to treatment with TCC was associated with the development of CNO related deformities. Adverse events related to treatment were not reported.[68]

Evidence Statement A: There is insufficient evidence to determine whether treatment of active CNO with non-removable device results in a shorter time to remission is achieved compared to a removable device.

QoE: Low

References: Fabrin et al. 2000,[72] Christensen et al. 2012,[70] Parisi et al. 2013,[73] Chantelau 2005,[51] Kimerle & Chantelau 2007,[68] Griffiths and Kaminski 2021,[67] Sinacore 1998,[74] de Souza 2008,[71] Fejvarova et al. 2005.[69]

Evidence Statement B: There is insufficient evidence to determine whether treatment of active CNO with a non-removable device in comparison with a removable device is associated with a lower risk of developing foot deformities.

QoE: Low

References: Fabrin et al. 2000,[72] Christensen et al. 2012,[70] Parisi et al 2013,[73] Chantelau 2005,[51] Kimerle & Chantelau 2007,[68] Griffiths and Kaminski 2021,[67] Sinacore et al. 1998,[74] de Souza 2008,[71] Fejvarova et al. 2005.[69]

Evidence Statement C: There is some, but conflicting, evidence suggesting that treatment of active CNO with a removable device can be associated with a very poor outcome (major amputation, foot surgery) as these poor outcomes were less frequently reported in patients treated with a non-removable TCC.

QoE: Low

References: Fabrin et al. 2000,[72] Parisi et al. 2013,[73] Christensen et al. 2012,[70] Chantelau 2005,[51] Kimerle & Chantelau 2007,[68] Griffiths and Kaminski 2021,[67] Sinacore 1998,[74] de Souza 2008.[71]

Evidence Statement D: Both removable and non-removable off-loading devices in the treatment for active CNO were in some studies but not all, associated with the development of foot ulcers and minor skin lesions.

QoE: Low

References: Fabrin et al. 2000,[72] Griffiths and Kaminski 2021,[67] Parisi et al. 2013,[73] de Souza 2008,[71] Fejfarova et al. 2005.[69]

Evidence Statement E: Given the lack of comparative studies and the limitations of observational studies there is insufficient evidence to determine whether a non-removable off-loading device is preferable to a removable device.

QoE: Low

References: Fabrin et al. 2000,[72] Parisi et al. 2013,[73] Christensen et al. 2012,[70] Chantelau 2005,[51] Kimerle & Chantelau 2007,[68] Griffiths and Kaminski 2021,[67] Sinacore 1998,[74] de Souza 2008,[71] Fejfarova et al. 2005.[69]

PICO 3: In a person with diabetes and active CNO, is a knee-high offloading device superior to a below ankle offloading device to achieve a shorter time to apparent remission and to prevent the development of complications?

Summary of the Evidence: n/a

Evidence Statement: No evidence was identified to determine whether a knee-high offloading device is superior to a below ankle offloading device regarding efficacy and complications.

Quality of Evidence (QoE): n/a

References: none

PICO 4: In a person with active CNO treated with an offloading device, is reduced weight bearing superior to weight bearing to achieve a shorter time to apparent remission and to prevent complications?

Summary of the Evidence: As previously discussed in this review, Sinacore's retrospective non-comparative case series evaluated healing time by foot location in 30 participants with active CNO.[74] Treatment consisted of TCC with initial 24 h of non-weight bearing followed by partial weight bearing with assistive devices (e.g., bilateral crutches) and instructions to limit regular weight bearing activities. Twenty-eight percent of patients complied with the treatment instructions. Patients who did not comply took an average of 34 days longer to achieve healing ($p < 0.05$).

Evidence Statement A: There is limited evidence suggesting that people treated with a non-removable TCC for active CNO and who followed advice to limit weightbearing and use bilateral crutches, had a shorter time to healing compared to those who did not.

QoE: Low

References: Sinacore 1998.[74]

Evidence Statement B: There is some evidence that the limitation of weight bearing during TCC treatment may reduce healing time.

QoE: Low

References: Sinacore 1998.[74]

Clinical Question: Can medical therapy in a person with diabetes mellitus and active CNO with intact skin result in shorter time to remission and prevent complications?

PICO: In a person with diabetes mellitus and active CNO, is treatment with bisphosphonates, calcitonin, denosumab, parathyroid hormone, methylprednisolone, or vitamin D, advised in addition to offloading compared to offloading alone to achieve a shorter time to apparent remission and to prevent complications?

Summary of the Evidence: Our systematic review identified eight studies on pharmacological intervention used in the management of active CNO. This included seven randomized control trials[35,75–80] and one cohort study.[81] For the risk of bias see Table 1.

These studies were sub-divided firstly into therapies that potentially inhibit bone resorption in the early inflammatory phase of the disease: bisphosphonates (alendronate, pamidronate, zolendronate),[76,78–80] calcitonin[75] and denosumab.[81] Secondly, into agents that could stimulate bone formation: parathyroid hormone (PTH)[35] and thirdly into anti-inflammatory therapies: methylprednisolone.[77]

Therapies that potentially inhibit bone resorption: Bharath et al.'s 2013 RCT, with a high risk of bias, compared 23 participants with active CNO treated with intravenous zoledronic acid with 22 with active CNO treated with alendronate.[76] The primary end point was complete clinical resolution of active CNO. No significant difference in time for complete clinical resolution was observed between the two groups. In Parkarinen et al's RCT, with high risk of bias, 18 patients with active CNO were treated with three intravenous infusions of 4 mg zoledronic acid for one month intervals to determine whether this treatment would shorten time to clinical resolution.[79] They compared these patients to a group of 17 patients with active CNO receiving a placebo treatment (of note, 2 patients in the treatment group and 1 in the control group had non-infected plantar ulceration). There was a significant increase in time to resolution in the zoledronic acid treatment group compared with placebo. In Pitocco et al's RCT, with high risk of bias, 11 patients with active CNO were treated with oral alendronate 70 mg once weekly and were compared to a group of 9 controls.[80] Of note, 5 participants had foot ulcerations that were not infected. The authors observed that alendronate treatment may be associated with a reduction in pain. In the double-blind randomized placebo-controlled trial of Jude et al 39 patients from four centres with active CNO received either a single infusion of 90 mg of pamidronate or placebo (saline).[78] This RCT had a low risk of bias. In comparison to controls, the group treated with pamidronate had a reduction in circulating and urinary markers of bone turnover and of pain. No differences were observed in the fall of foot temperature between both groups. Time to remission and foot deformities were not reported.

Bem et al's RCT (high risk of bias) studied the effect of intranasal calcitonin on bone metabolism and disease activity in patients with active CNO during a 6-month treatment period.[75] Participants were randomized to receive nasal spray of salmon calcitonin 200 IU daily with oral calcium supplementation (study group) or calcium supplementation only (control). The authors did not observe any effect on time to remission during the 6 months of follow-up.

TABLE 1 Risk of bias table for intervention randomized controlled trials (RCTs).

RCTs Intervention	Randomisation	Independent assign-ment	Patient/care provider blinded	Outcome assessor blinded	Similarity groups	With-drawal/ drop-out acceptable (<20%)	Intention-to-treat	Patients treated equally except for intervention	Selective reporting ruled out	Free from commercial interest	Score
Bone resorption inhibitors											
Bisphosphonates											
Bharath et al, 2013	-	?	-	-	+	+	-	+	+	+	5/10
Jude et al, 2001	+	+	+	+	+	+	+	?	+	+	9/10
Pakarinen et al, 2011	+	?	?	?	+	+	-	?	-	+	4/10
Pitocco et al, 2005	+	?	?	?	?	?	?	+	-	+	3/10
Calcitonin											
Bem et al, 2006	+	?	-	?	+	?	?	+	-	+	4/10
Anti-inflammatory											
Methyprednisolone											
Das et al, 2019	+	?	+	?	+	?	?	+	?	+	5/10
Bone formation stimulation											
PTH 1–84											
Petrova et al 2021	+	+	+	+	+	?	+	+	+	+	9/10
Cohort studies Intervention		**Selection bias avoided/ excluded**	**Intervention clearly defined**	**Outcome clearly defined**	**Outcome assessed blind for exposure**	**Withdrawal/ drop-out acceptable (<20%)**	**Selective loss to follow-up excluded**	**Major confounders/ prognostic factors identified and controlled**	**Selective reporting ruled out?**	**Free from commer-cial interest ?**	**Score**
Bone resorption inhibitors											
Denosumab											
Busch-Westbroek et al, 2018	+	-	+	+	?	?	?	-	-	+	4/10

Busch-Westbroek et al. in 2018 reported an exploratory, open label cohort study with high risk of bias that compared the outcomes of 11 subjects with active CNO who were treated with a single injection denosumab 60 mg subcutaneously to a group of 11 historic control subjects with active CNO not treated with denosumab.[81] It should be noted that five out of the eleven subjects in the historic control group had also been treated with alendronate. In comparison to the historic control group, a single injection of denosumab was associated with a faster time to remission, shorter duration of total contact cast treatment (approximately 1 ½ month shorter) and less malalignment at the Chopart-Lisfranc joint. Also, time to fracture healing on radiographs was shortened by approximately 2 months compared to the control group.

Therapies that could stimulate bone formation: Petrova et al. 2021 reported an RCT with low risk of bias that evaluated 26 patients with active CNO treated with 100 mg PTH (1–84) (1–84) and compared them to a group of 22 control patients.[35] The treatment group received 100 mg PTH (1–84) subcutaneously daily and the control group placebo once daily in identical syringes until resolution of active CNO or up to 12 months. Treatment with PTH 1–84 did not improve time to remission, fracture healing or prevention/progression of foot deformity.

Anti-inflammatory therapies: Das et al. in 2019 performed an open label RCT with high risk of bias[77]; the outcome of three groups were compared. Treatment group A consisted of 11 subjects treated with methylprednisolone 1 g, group B of 12 subjects treated with zoledronic acid 5 mg and the control group consisted of 13 subjected treated with a saline placebo. All subjects were treated once a month for 3 months. The treatment with methylprednisolone was associated with a longer time to remission compared to both zolendronate acid and placebo treatment. Two patients developed acute kidney injury.

Evidence Statements (*based on outcome; see* Table 2):

Outcome: Time to Remission

Evidence Statement: Treatment with alendronate, pamidronate, zolendronate, calcitonin, denosumab, PTH (1–84), and methylprednisolone seems not to be associated with a shorter time to remission.

Quality of Evidence (QoE): Low

References: Bem et al. 2006,[75] Busch-Westbroek et al. 2018,[81] Das et al 2019,[77] Jude et al. 2001,[78] Pakarinen et al. 2011,[79] Petrova et al. 2021[35] Pitocco et al. 2005[80]

Outcome: Development/progression of foot deformity

Evidence Statements: 1. Treatment with denosumab may be associated with a reduction in foot deformity. 2. Treatment with PTH may not be associated with a reduction in foot deformity.

Quality of Evidence (QoE): Low

References: Busch-Westbroek et al. 2018,[81] Petrova et al. 2021[35]

Outcome: Radiological facture healing

Evidence Statements: 1. Treatment with denosumab may be associated with faster fracture healing. 2. Treatment with PTH may not be associated with faster fracture healing.

Quality of Evidence (QoE): Low

References: Busch-Westbroek et al. 2018,[81] Petrova et al. 2021[35]

Outcome: Reduction in pain

Evidence Statement: Treatment with alendronate or pamidronate may be associated with a reduction in pain.

Quality of Evidence (QoE): Low

References: Jude et al. 2001,[78] Pitocco et al. 2005[80]

Outcome: Loss of kidney function

Evidence Statement: Zolendronate infusions may be associated with loss of kidney function.

Quality of Evidence (QoE): Low

References: Das et al. 2019[77]

Clinical Question: In a person with diabetes mellitus and active Charcot neuro-osteoarthropathy (CNO) with intact skin, is

TABLE 2 Medical therapy: Evidence statement based on outcome.

Outcome	Evidence statement	Quality of evidence	References
Time to remission	Treatment with alendronate, pamidronate, zolendronate, calcitonin, denosumab, parathyroid hormone (1–84) and methylprednisolone seem not to be associated with shorter time to remission.	Low	Bem, R., et al. (2006), Busch-Westbroek, T., et al. (2018), Das, L., et al. (2019), Jude, E., et al. (2001) Pakarinen, T., et al. (2011), Petrova, N. et al. (2021) Pitocco, D., et al. (2005)
Development/progression of foot deformity	1. Treatment with denosumab may be associated with a reduction in foot deformity. 2. Treatment with parathyroid hormone may not be associated with a reduction in foot deformity.	Low	Busch-Westbroek, T. et al. (2018), Petrova, N. et al. (2021)
Radiological fracture healing	1. Treatment with denosumab may be associated with faster fracture healing. 2. Treatment with parathyroid hormone may not be associated with faster fracture healing.	Low	Busch-Westbroek, T. et al, et al. (2018), Petrova, N. et al. (2021)
Reduction in pain	Treatment with alendronate or pamidronate may be associated with a reduction in pain.	Low	Jude, E. et al. (2001),Pitocco, D. et al. (2005)
Loss of kidney function	Zolendronate infusions may be associated with loss of kidney function.	Low	Das, L., et al. (2019)

reconstructive surgery associated with a shorter time to remission, prevention of deformity development, and prevention of deformity progression compared to no surgery?

PICO: In a person with diabetes mellitus and active CNO is surgery associated with a shorter time to apparent remission, prevention of deformity development, and prevention of deformity progression compared to no surgery?

Summary of the Evidence: We identified one observational retrospective study that evaluated the outcomes of patients with active CNO and intact skin who underwent surgical intervention for the treatment of active CNO.[18] Simon et al reported on 14 patients with active CNO who underwent open reduction and primary realignment arthrodesis of the tarsal-metatarsal region with autologous bone graft. This study included 43 patients with active CNO, of which 29 were treated with TCC immobilisation. The remaining 14 patients who underwent surgery requested surgical intervention as an alternative to the standard TCC treatment. The patients in the surgical treatment group were reported to have had knowledge of the consequences related to foot deformity development. The mean time to assist weight bearing was 10 weeks and the mean time to unassisted weightbearing was 15 weeks. All 14 patients had successful surgical procedures with no reported complications during the mean follow-up of 41 months (range, 25.3–77.3 months). All surgically treated patients returned to their pre CNO activity level. This study was limited to only 14 patients with active CNO of the tarsometatarsal joints.

Evidence Statement: There is no evidence that demonstrates surgery is associated with a shorter time to apparent remission and prevention of deformity progression compared to the standard of care offloading.

QoE: Very low

References: Simon et al 2000[18]

3.4 | Prevention of re-activation

Clinical Question: In persons with diabetes mellitus and active Charcot neuro-osteoarthropathy (CNO) with intact skin who have been treated and are in remission, is therapeutic footwear preferred to conventional footwear to prevent re-activation of the disease?

PICO: In a person with diabetes mellitus and CNO who have been treated and are in apparent remission, is therapeutic footwear preferred to conventional footwear to prevent re-activation of active CNO?

Summary of the Evidence: We did not find any published evidence to answer this PICO.

Evidence Statement: We identified no evidence that demonstrates therapeutic footwear is superior to conventional footwear to prevent re-activation of active CNO.

Quality of Evidence (QoE): n/a

References: none

4 | DISCUSSION

This is the first systematic review conducted by the IWGDF on the diagnosis and treatment of active CNO in persons with diabetes mellitus and intact skin. We aimed to identify studies relevant to the diagnosis and treatment of active CNO in persons with diabetic neuropathy. We also sought to identify studies focused on remission and prevention of re-activation in those who had been treated and were no longer in the active CNO state. We identified a total of 37 studies for our 4 categories of PACO/PICOs; 14 studies relevant to Diagnosis, 18 for Treatment and 5 studies for Identification of Remission. We did not identify studies that met inclusion criteria for Prevention of Re-activation.

4.1 | Diagnosis

Fourteen studies relevant to the diagnosis of active CNO with respect to clinical examination, imaging and laboratory testing in patients with intact skin were included. All were retrospective and observational studies. We did not identify any studies that demonstrated the accuracy of clinical examination findings using imaging as a comparator to predict or diagnose active CNO. One retrospective case series compared foot skin temperature measurements using dermal infrared thermometry in patients with active CNO and patients with asymptomatic sensory neuropathy,[50] but no studies determined diagnostic accuracy and which temperature values are indicative of active CNO. This was a striking observation as many publications use the cut-off value of the left-right foot temperature difference of 4˚ Fahrenheit (2.2˚Celsius) to diagnose the disease. This value is therefore not grounded on clinical evidence despite this being a relatively simple and attractive method. Further research is necessary to determine the diagnostic accuracy of temperature measurements and which cut-off value to use in clinical practice. In regard to imaging for the diagnosis of active CNO, we identified seven retrospective studies: four focused on MRI and three focused on nuclear imaging.[24,51–56] Although the quality of studies was low, MRI demonstrated high sensitivity to confirm a diagnosis of active CNO in patients with an intact skin and clinical suspicion of the disease.[51–54] We identified six observational studies on the diagnostic value of the serologic markers CRP, ESR, WBC and alkaline phosphatase in patients with active CNO.[40,57–61] We did not find evidence to show that any blood laboratory test can diagnose or exclude active CNO.

4.2 | Treatment

We identified 18 studies relevant to the treatment of active CNO. Treatment studies included those focused on offloading (total contact cast, removable/non-removable knee high devices), medical/pharmacological treatment (bisphosphonates, calcitonin, denosumab, PTH,

methylprednisolone), and surgical treatment in the setting of active CNO. For offloading and medical/pharmacological treatment, studies including people with non-infected feet were included only if it was deemed by the authors that the presence of ulceration would not impact the treatment. Surgical treatment included only studies of patients with active CNO and intact skin. We identified nine studies focused on offloading; three retrospective case series,[51,67,69] five retrospective non-comparative case series[70–72] and one case control study,[68] all with low quality of evidence. Although the quality of evidence was low, total contact cast immobilisation traditionally has been the "gold standard" offloading treatment for active CNO. We identified eight pharmacological treatment studies; seven RCTs[35,75–80] and one cohort study.[81] Based on these studies, we found no evidence to support the use of pharmacological interventions to treat active CNO. We identified only one retrospective cohort study for surgical intervention in patients with active midfoot CNO and intact skin.[18]

4.3 | Identification of remission

Five observational studies were identified regarding the identification of remission in patients who had been treated for active CNO.[62–66] Two studies reported the predictive value using infrared thermometry to monitor and identify remission based on clinical findings.[23,25] The remaining studies used MRI to identify remission and also reported foot skin temperature measurement.[24,26,27] A major concern of these five studies is that none of the five reported the sensitivity or specificity of using skin foot temperature to identify remission, either in isolation or compared to imaging. In addition, in some studies the presence of ulceration was not specified. Furthermore, one study found that 23% of patients demonstrated clinical signs of healing 3–6 months prior to healing as defined by MRI.[63]

4.4 | Prevention of re-activation

We did not identify any studies that met our inclusion criteria for the prevention of re-activation in patients who had been previously treated for active CNO and were in remission. Specifically, we did not identify any evidence that demonstrated therapeutic footwear to be superior to conventional footwear to prevent re-activation of active CNO. The members of the working group recognise that certain patients with CNO may require some form of therapeutic footwear to accommodate deformity and that, as described in our guideline, patients should be gradually mobilised once the disease is in remission in order to prevent re-activation.[10]

5 | CONCLUSIONS

Our systematic review demonstrates that there is a paucity of high-quality data on the diagnosis, treatment, and prognosis of active CNO in people with DM and intact skin. Further research is warranted to address the issues surrounding this complex disease. We encourage our colleagues who care for patients with CNO to consider developing some form of surveillance (e.g., registries and pathways) to monitor and attempt to improve outcomes in patients with CNO. We encourage our research colleagues to consider key controversial areas as a platform to conduct well-designed studies in different areas of CNO. Future research should address both non-surgical and surgical managements to better inform the diabetic foot community on the most effective treatment for patients with diabetes mellitus and CNO.

AUTHOR CONTRIBUTIONS

Katherine M. Raspovic, Dane K. Wukich and Nicolaas C. Schaper assisted Helen Mayo who designed the search strings and performed the literature search. Katherine M. Raspovic and Dane K. Wukich performed the title/abstract screening and full text reviews for eligibility. Katherine M. Raspovic wrote the manuscript and acted as the secretary of the Working Group. Dane K. Wukich co-wrote the manuscript and acted as the chair of the Working Group. Katherine M. Raspovic, Nicolaas C. Schaper, Catherine Gooday and Dane K. Wukich extracted data from the included studies. Robert Bem, Mary Hastings, Crystal Holmes, Nina L. Petrova, and Maria Gala Santini Araujo contributed to the data extraction. Nicolaas C. Schaper and Catherine Gooday assessed the medical treatment studies for methodological quality and risk of bias. Katherine M. Raspovic, Nicolaas C. Schaper, Catherine Gooday, Arun Bal, Robert Bem, Avneesh Chhabra, Mary Hastings, Crystal Holmes, Nina L. Petrova, Maria Gala Santini Araujo, Eric Senneville and Dane K. Wukich assessed the literature, drew conclusions, drafted and agreed upon the evidence statements and critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

All individual conflicts of interest can be found at https://iwgdfguidelines.org/charcot/.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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