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Guidelines on the diagnosis and treatment of active Charcot neuro-osteoarthropathy in persons with diabetes mellitus (IWGDF 2023)

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Abstract

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This is the first guideline on the diagnosis and treatment of active Charcot neuro-osteoarthropathy in persons with diabetes published by the IWGDF. We followed the GRADE Methodology to devise clinical questions in the PACO (Population, Assessment, Comparison, Outcome) and PICO (Population, Intervention, Comparison, Outcome) format, conducted a systematic review of the medical literature, and developed recommendations with the rationale. The recommendations are based on the evidence from our systematic review, expert opinion when evidence was not available, and also taking into account weighing of the benefits and harms, patient preferences, feasibility and applicability, and costs related to an intervention. We here present the 2023 Guidelines on the diagnosis

Abbreviations: AFO, ankle foot orthosis; CNO, Charcot neuro-osteoarthropathy; CROW, Charcot Restraining Orthotic Walker; CT, computed tomography; IWGDF, International Working Group on the Diabetic Foot; MRI, Magnetic Resonance Imaging; PTH, parathyroid hormone.

and treatment of active Charcot neuro-osteoarthropathy in persons with diabetes mellitus and also suggest key future topics of research.

KEYWORDS
Charcot foot, Charcot neuro-osteoarthropathy, Charcot neuroarthropathy, Charcot osteoarthropathy, diabetic foot, guidelines

1 | RECOMMENDATIONS

1.1 | Diagnosis

1. Always consider active Charcot neuro-osteoarthropathy in a person with diabetes mellitus, neuropathy and intact skin when there are clinical findings of an increase in temperature, oedema, and/or redness of the foot, compared to the contralateral foot. Best Practice Statement.
2. Consider using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected Charcot neuro-osteoarthropathy with intact skin, using a standardised approach to the measurement of temperatures to allow for more accurate comparison over time (GRADE recommendation: Conditional; Certainty of the evidence: Low).
3. When using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin, consider calculating temperature difference between both legs, using the highest temperature on the affected foot or ankle in comparison with the same anatomic point on the contralateral extremity (Conditional; Low).
4. In a person with diabetes mellitus with bilateral active Charcot neuro-osteoarthropathy (CNO) and intact skin or with unilateral CNO and intact skin in the absence of the contralateral limb, ascending temperature gradients (toe-knee) may be useful for comparison over time. Best Practice Statement.
5. Initiate knee high immobilisation/offloading promptly while further diagnostic studies are performed to confirm or rule out active Charcot neuro-osteoarthropathy (CNO) when active CNO is suspected in a person with diabetes mellitus and intact skin (Strong; Low).
6. Perform plain X-ray of the foot and ankle in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. Ideally, bilateral plain X-rays should be performed, if possible, for comparison purposes. Best Practice Statement.
7. Perform X-rays that include the anteroposterior (AP), medial oblique, and lateral projections in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. The ankle and foot views should include the AP, mortise, and lateral projections. Ideally, standing (also known as 'weight- bearing') radiographs should be performed. If a patient is not able to bear weight on their feet, non-weight-bearing radiographs are an alternative, but may not demonstrate malalignments that are more apparent in the standing position. Best Practice Statement.
8. Perform Magnetic Resonance Imaging in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with normal appearance of the plain X-rays to diagnose or exclude the disease and its activity (Strong, Moderate).
9. If Magnetic Resonance Imaging is unavailable or is contra-indicated in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy, consider a nuclear imaging scan (scintigraphy), CT (computed tomography) scan, or SPECT-CT (Single Photon Emission Computerised Tomography) to support the diagnosis of active Charcot neuro-osteoarthropathy (Conditional; Low).
10. We suggest not using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count, alkaline phosphatase, or other blood tests in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin to diagnose or exclude the disease (Conditional; Low).

1.2 | Identification of remission

11. Consider the measurement of skin temperature of the affected and unaffected limb with serial examinations to monitor disease activity in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin (Conditional, Low).
12. We suggest not using soft tissue oedema alone to determine when active Charcot neuro-osteoarthropathy is in remission (Conditional; Low).
13. We suggest that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that active Charcot neuro-osteoarthropathy is in remission (Conditional; Low).
14. We suggest that the frequency of appointments for assessing disease activity in active Charcot neuro-osteoarthropathy should depend on specific factors such as fluctuation in oedema volume, co-morbidities, the risks associated with treatment and recovery, access to assistance with home treatment needs, and a person's progress and recovery (Conditional; Low).

1.3 | Treatment

15. Use a non-removable knee-high device to immobilise and offload the foot to promote the remission of the disease, and prevention or progression of deformity in a person with active Charcot neuro-osteoarthropathy and intact skin (Strong; Low).

16. Consider using a total contact cast in the treatment of active Charcot neuro-osteoarthropathy with intact skin in a person with diabetes mellitus. A knee-high walker rendered non-removable can be considered as a second choice in order to immobilise and offload the foot (Conditional; Low).
17. A removable knee-high device worn at all times can be considered as the third treatment choice in a person with diabetes mellitus, active Charcot neuro-osteoarthropathy and intact skin of the foot for whom a non-removable knee-high offloading device is contraindicated or not tolerated (Conditional; Low).
18. We suggest not to use a below the ankle offloading device (e.g. surgical shoe, postoperative sandal, custom moulded shoe, or slipper cast) in the treatment of active Charcot neuro-osteoarthropathy and intact skin, given the inadequate immobilisation of the diseased bone and joints, and limited off-loading capacity (Conditional; Low).
19. Treatment with a knee-high offloading device should be considered as soon as possible once the diagnosis of active Charcot neuro-osteoarthropathy is considered (Strong; Low).
20. In a person with active Charcot neuro-osteoarthropathy who is being treated with a knee-high device, we suggest using assistive devices to reduce weight-bearing on the affected limb (Conditional; Low).
21. Do not use alendronate, pamidronate, zoledronate, calcitonin, PTH, or methylprednisolone as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin (Strong; Moderate).
22. We suggest not to use denosumab as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin (Conditional; Low).
23. We suggest evaluating the need for vitamin D and calcium supplementation in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin during the phase of fracture healing, in doses according to (inter)national guidelines on supplementation in persons at risk of vitamin D deficiency and/or those with insufficient calcium intake (Conditional, Low).
24. In a person with active Charcot neuro-osteoarthropathy and intact skin, and with instability of foot and ankle joints, and/or deformity with a high-risk of developing ulcer in the offloading device, or pain that cannot be sufficiently stabilised in a total contact cast or a non-removable knee-high device, we suggest that surgical intervention should be considered (Conditional; Low).

1.4 | Prevention of re-activation

25. Footwear and/or orthoses that best accommodate and support the shape of the foot/feet and ankle to help prevent re-activation of Charcot neuro-osteoarthropathy (CNO) are recommended in a person with diabetes mellitus, intact skin, treated for active CNO with an off-loading device and who is now in remission (Strong; Moderate).
26. When deformity and/or joint instability is present, in order to optimise the plantar pressure distribution, below the knee customised devices should be used for additional protection in a person with diabetes mellitus, intact skin, treated for active Charcot neuro-osteoarthropathy who is now in remission (Strong; Moderate).

2 | INTRODUCTION

According to current insights, Charcot neuro-osteoarthropathy (CNO) is viewed as an inflammatory process in persons with peripheral polyneuropathy which results in injury to bones, joints, and soft tissues. Most commonly, CNO occurs in people with diabetes mellitus and involves the foot and ankle although it can occur in anyone with peripheral neuropathy. The soft tissue and osseous injury in individuals with neuropathy may result in distortion of the architecture of the foot and ankle and long-term deformity because of fractures, dislocations, and fracture-dislocations. The true incidence and prevalence of CNO in diabetes mellitus are unknown, largely because the absence of pain from peripheral neuropathy often impacts the timing of presentation to healthcare providers. Previous studies of several populations have reported prevalence rates ranging from 0.04% of patients with diabetes mellitus at seven foot care specialist centres in England,[1] to 0.3% of patients with diabetes mellitus at a regional referral centre in Ireland,[2] to 0.53% of all people with diabetes mellitus in a national registry study in Denmark.[3] The International Diabetes Foundation has estimated that 537 million adults worldwide were living with diabetes in 2021. Using a prevalence of 0.3%, this estimates that approximately 1.6 million people worldwide are living with CNO, with an annual incidence of 160,000 new cases per year.[4] To put this in a global perspective, in 2020, the estimated number of new cases of melanoma per year (320,000) were only twice that of CNO, and the new cases of Hodgkin's lymphoma (83,000) were half of the CNO.[5]

Numerous studies have found that patient-reported health-related quality of life is negatively impacted by CNO.[6–9] Furthermore, after the resolution of the inflammatory phase CNO can result in permanent deformity of the foot and/or ankle. Bone and joint deformities, as a consequence of active CNO, predispose to ulceration and infection, both of which significantly increase the risk of major lower extremity amputation. Studies have identified a six to 12 times increased risk of major amputation in individuals with a foot ulcer that is the consequence of a CNO deformity as compared to those without an ulcer.[10,11] A major amputation can have a profound impact on the individual, their families and society. In many cases, people who have undergone major amputation can no longer work, and this has financial consequences for the individual and their families.[12] In addition to the impact on quality of life, a recent study collected data from studies published following 2007 and calculated a pooled mean 5-year mortality of 29% in patients with CNO.[13]

Improved understanding of the pathophysiology of CNO has occurred over the past 2 decades. It is assumed that some form of trauma, either perceived or not perceived,[14] provokes an acute inflammatory response in the foot and/or ankle of persons with peripheral neuropathy. Disproportionate release of proinflammatory and anti-inflammatory cytokines results in activation of nuclear factor-κB (NF-κB) via the receptor activator of nuclear factor-κβ ligand-(RANK-L) pathway, which stimulates osteoclastogenesis.[15,16] In the inflamed foot, there is targeted recruitment, proliferation and differentiation of osteoclastic precursors into highly aggressive osteoclasts with enhanced resorbing activity in response to RANKL and TNF-α.[17,18] This inflammatory process, in combination with the mechanical forces applied during ambulation on a neuropathic foot, can lead to disruption or weakening of ligaments, joint dislocations and/or fractures of the foot/ankle. Another important component of the pathophysiology of active CNO involves the potential role of genetics. Genes of the osteoprotegerin/RANKL/RANK axis and their single-nucleotide polymorphisms are possibly additional risk factors for the development of CNO.[19–21]

At the current time there are uncertainties about diagnostic criteria, optimal treatment methods, pharmacologic intervention, monitoring, and identification of remission of CNO. The aim of this new guideline of the International Working Group on the Diabetic Foot (IWGDF) on CNO is to provide evidence-based recommendations on the diagnosis and management of active CNO of the foot with intact skin in persons with diabetes mellitus. This guideline also includes a rationale of how we came to each recommendation based on our systematic review of the literature which is published in parallel,[22] together with a consideration of the benefits and harm, patients' values and preferences, and the costs related to each intervention. We also propose an agenda for future research. This guideline on CNO is part of the IWGDF guidelines on the prevention and management of diabetic foot disease.[23–29]

3 | TARGET POPULATION AND TARGET AUDIENCE

The primary target population of this guideline is persons with diabetes mellitus and active CNO, with intact skin. The primary target audience of this guideline are all health care professionals who are involved in the diagnosis and treatment of persons with CNO and diabetes mellitus.

4 | BACKGROUND: DEFINITIONS AND TERMINOLOGY

The following section is a background summary on the definitions of the disease and the terminology used for the purposes of this guideline. Due to insufficient high-quality evidence this section on definitions is primarily based on expert opinion.

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.

Active Charcot neuro-osteoarthropathy: Active CNO is the presence of a red, warm, swollen foot with osseous abnormalities on imaging in a person with diabetes mellitus and neuropathy. During the course of the disease, as long as there are signs of inflammation in the affected foot, the CNO is presumed to be 'active.'

Charcot neuro-osteoarthropathy in clinical remission: The absence of clinical signs of inflammation, with or without deformity, and radiographic consolidation of fractures, if present, on plain X-ray. Remission is synonymous with the 'inactive' stage of CNO.

Re-activation of Charcot neuro-osteoarthropathy: A repeat 'episode'/return of symptoms in the ipsilateral foot after the resolution of the original active CNO event. If active CNO develops in the contralateral foot, that should be considered a 'new' CNO event and not re-activation.

Stage 0 active CNO: Person with diabetes mellitus and neuropathy who presents with clinical signs of active CNO and normal plain X-rays. In this stage, plain X-rays are considered normal but demonstrable osseous abnormalities will be present on Magnetic Resonance Imaging (MRI).[30,31]

Offloading: The relief of mechanical stress (pressure) from the bones and joints of the affected foot during standing or walking. For purposes of this guideline, offloading should not be interpreted as complete non-weightbearing.

The recommendations in this guideline are focused on the individual with active CNO and intact skin. During the course of the disease, as long as there are signs of inflammation in the affected foot, the CNO is presumed to be 'active'. As will be further discussed in this document, there is no 'gold standard' test to diagnose active CNO. Therefore, both clinical signs of inflammation as well as signs of bone or joint injury/abnormalities on imaging studies such as plain X-ray or MRI have to be present in order to make a definitive diagnosis. Remission is synonymous with the inactive stage of CNO. As discussed below, it usually takes several months of offloading/immobilisation before the clinical signs of active CNO have resolved and the fractures have healed. If at that stage offloading therapy is stopped and the patient starts walking in inappropriate footwear, there is a chance of reactivation of the disease process with the risk of development of new fractures or worsening of an existing deformity. For this reason, we choose the terminology 'in remission' instead of 'healed'.

5 | METHODS

For these guidelines, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology was followed. The GRADE System is structured by the development of clinical questions in the PACO (Population, Assessment, Comparison, Outcome) and PICO (Population, Intervention, Comparison, Outcome)

format, systematic review, and assessment of the available evidence. After assessment of the evidence, recommendations are developed with their supporting rationale.[32,33] In specific situations when reviewers were authors of papers under consideration, the authors recused themselves to reduce the risk of bias in assessments and selection of articles.

To begin this process, an international, multidisciplinary working group of experts in this field (the authors of this guideline) was installed by the IWGDF Editorial Board. The working group developed the clinical questions to be investigated after consultation with external experts from diverse geographic locations as well as a patient representative. Critically important outcomes for clinical questions focused on intervention were formulated and voted by the working group members as deemed necessary. Subsequently, PACOs and PICOs were created which were reviewed by the IWGDF Editorial Board.

Next, a systematic review of the literature was performed to address the clinical questions. The systematic review for this guideline is published as a separate document.[22] 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 influence the outcomes. For each clinical question the certainty of evidence was graded and then rated as 'high,' 'moderate,' or 'low'.[34]

Finally, recommendations were formulated to address each clinical question based on the evidence from the systematic review. Using the GRADE system, rationale was provided for how we determined each recommendation. The rationale was based on the evidence from the systematic review[22] and expert opinion when evidence was not available. The strength of each recommendation was graded as 'strong' or 'conditional'. 'Best Practice Statements' were developed when the certainty of the desirable effects of an intervention clearly outweighed its undesirable effects in the situations where the available evidence was indirect.[35] The recommendations and corresponding rationales were reviewed by the same international external experts and IWGDF Editorial Board who initially reviewed the PACOs and PICOs. A summary of judgement table was created for each intervention recommendation based on the GRADE approach[34] (See Appendix 1). The framework for each judgement table included a column for criteria, judgements, and impact of the intervention. For a more detailed description of the methodology and writing of these guidelines, please refer to the IWGDF Guidelines development and methodology document.[36]

5.1 | Conflict of interest statement

The Charcot guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included ownerships of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups and these can be found at www.iwgdfguidelines.org. No company was involved in the development or review of the guideline. Nobody involved in the guideline development received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting in-person.

6 | RECOMMENDATIONS

In this guideline, the recommendations for the diagnosis and treatment of active CNO in persons with diabetes mellitus and intact skin are discussed based on the following categories: Diagnosis, Identification of Remission, Treatment, and Prevention of Re-Activation. First, we formulated clinical questions and subsequently using the PACO and PICO format a systematic review of the literature was performed based on these clinical questions.[22] We identified a total of 37 studies; 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. After completion of the systematic review, evidence statements were developed based on the available literature.[22] We subsequently formulated the following 26 recommendations.

6.1 | 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?

Recommendations

1. Always consider active Charcot neuro-osteoarthropathy in a person with diabetes mellitus, neuropathy and intact skin when there are clinical findings of an increase in temperature, oedema, and/or redness of the foot, compared to the contralateral foot. Best Practice Statement.

2. Consider using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected Charcot neuro-osteoarthropathy with intact skin, using a standardised approach to the measurement of temperatures to allow for more accurate comparison over time (Conditional; Low).
3. When using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin, consider calculating temperature difference between both legs, using the highest temperature on the affected foot or ankle in comparison with the same anatomic point on the contralateral extremity (Conditional; Low).
4. In a person with diabetes mellitus with bilateral active Charcot neuro-osteoarthropathy (CNO) and intact skin or with unilateral CNO and intact skin in the absence of the contralateral limb, ascending temperature gradients (toe-knee) may be useful for comparison over time. Best Practice Statement
5. Initiate knee high immobilisation/offloading promptly while further diagnostic studies are performed to confirm or rule out active Charcot neuro-osteoarthropathy (CNO), when active CNO is suspected in a person with diabetes mellitus and intact skin (Strong; Low).

Rationale

Active CNO should always be suspected when a person with diabetes and neuropathy presents with a unilateral red, warm, swollen foot, intact skin, and no history of ulceration. CNO left untreated presents a high risk of developing bone fractures, dislocations, deformity, ulceration, infection and even amputation with major lifelong consequences.[37,38] Clinical signs of inflammation, such as hyperaemia, increased foot skin temperature and oedema should be present when the diagnosis of active CNO is considered, after the exclusion of other diagnoses such as infection, gout, and deep venous thrombosis. Pain may be absent or relatively mild due to sensory neuropathy.[39] However, there are some individuals who present with more severe pain despite having peripheral neuropathy. Based on these arguments the Guideline committee formulated a Best Practice Statement, that is, that the disease should always be suspected in a hot swollen foot in a person with diabetes mellitus due to the severe consequences that may develop if this disease is left untreated such as fracture, dislocation, development of deformity, ulceration, infection and loss of limb.

In healthy individuals there is symmetry in skin foot temperature, but in the presence of inflammation this symmetry is lost and the temperature difference between both feet can be a more reliable measure than an isolated, unilateral measure.[40] In one retrospective study in people with active CNO, the site of maximum skin temperature difference between the affected and unaffected foot correlated with the radiographic imaging at diagnosis in 92% of cases (and during follow-up in 72% of cases).[35] When local radionucleotide uptake was measured with quantitative bone scans in individuals with active CNO, the difference in local skin temperature correlated with this uptake.[41] This suggests that skin temperature can be viewed as a proxy measure of the underlying active disease process in those with CNO.[41] Initially this temperature difference was assessed by palpation, but in recent decades several studies reported the use of handheld dermal infrared thermometry devices to diagnose CNO. Our systematic review could not identify studies demonstrating the diagnostic accuracy of such measurement when using radiological imaging and/or scintigraphy as a comparator in persons with active CNO.[22] We identified one retrospective case series of patients with diabetes that compared foot skin temperature measurements using dermal infrared thermometry in patients with active CNO and patients with asymptomatic sensory neuropathy.[42]

An increase in skin temperature of 2° Celsius or 4° Fahrenheit (which is actually 2.2° Celsius) of the involved foot compared to the same location on the uninvolved foot has been used as a diagnostic threshold for active CNO in several publications.[43] Our systematic review could not identify studies demonstrating the diagnostic accuracy of such measurement when using imaging as a comparator for the diagnosis of active CNO, however, there is evidence in regard to elevated temperature as a sensitive indicator of inflammation in diabetic feet and a precursor to ulceration.[22] In the absence of other signs and symptoms of inflammation (i.e. redness and swelling), an isolated increase in foot temperature may not always be indicative of active CNO and should be interpreted in the context of other clinical findings.[44,45] Although an essential part of the diagnostic evaluation, isolated elevation of foot skin temperature is not sufficient to diagnose or rule out active CNO. Consequently, unilateral asymmetric temperature elevation is sensitive but not specific in diagnostic active CNO.

There is no evidence to define which method/protocol for infrared skin temperature measurement is most accurate to diagnose active CNO and where, that is, on which anatomical locations, these measurements should be performed. A recent cohort study of 32 people with active CNO reported good intra- and inter-rater reliability of skin foot temperatures measured by infrared thermometry, but did not address uncertainties around the diagnostic accuracy of this technique.[46] There is uncertainty about the accuracy of existing thermometers[47] and if contact or non-contact thermometry devices should be preferred.[48] There is limited information on normative values of skin temperature in the neuropathic foot, and whether current thermometry devices are valid for these temperature ranges,[45] and factors such as the influence of ambient temperature and the acclimatization time that is needed after the footwear and socks are removed. The presence of concomitant ulceration and/or infection can also limit the usefulness of foot temperature to monitor CNO.[35] The use of the uninvolved foot as a comparator can probably overcome some, but not all, of these problems because the contralateral foot can be affected by diseases that influence skin temperature. The presence of bilateral active CNO disease will reduce the reliability of the temperature difference.

Despite the uncertainties, infrared thermometry currently seems to be preferable to assess foot skin temperature in order to calculate

the temperature difference between both feet as this is objective and measurable.[49] In the presence of bilateral foot disease or in the absence of the contra-lateral limb (i.e., amputation), calculating such a temperature difference is not feasible or possible. In these circumstances the increase in temperature due to the inflammatory process can probably be detected by comparing the distal temperature in the foot to the more proximal temperature in the lower and upper leg. We could not identify any studies that evaluated ascending temperature gradients in our systematic review. As detecting a locally elevated temperature is an important component in diagnosis and follow up, the Working Group suggests measuring ascending temperature gradients (toe-knee in the aforementioned circumstances. All members of the Working Group use this approach when bilateral measurements are not possible, but studies supporting this approach are lacking and therefore we made this a Best Practice Statement. Infrared thermometry is a relatively simple, inexpensive, and objective method to monitor changes over time, as discussed in the section Identification of Remission. To allow for more accurate comparison between visits we advise a standardised approach regarding acclimatization period, number and location of skin sites to be tested, and with which the temperature measurement technique should be used. Finally, in the absence of access to quantitative tools that assess foot temperature, clinicians should rely on using hand palpation to assess temperature difference. The benefits of assessing temperature, either with handheld thermometry devices or by palpation, are not associated with any risk of harm to the patient. We recognise that equity and feasibility can be impacted because not everyone treating patients with CNO will have access to a handheld device. Health equity, as it relates to this guideline, is when everyone has a fair and equal opportunity to attain their highest level of health despite their social, economic, cultural or geographic differences. Finally, we recognise that selection bias may be present in the studies which report on the efficacy of temperature assessment of handheld thermometry devices due to the variability of the studies.

Knee high immobilisation/offloading should be initiated immediately when active CNO is suspected in a person with diabetes mellitus and intact skin. Early detection, immobilisation and reduced weight-bearing on the diseased foot has been shown to minimise the development of deformity.[37,38] Evidence for this recommendation is low but withholding offloading therapy in a person with a suspected serious disease puts this person unnecessarily at risk of the dire consequences of untreated disease which is why we graded this as 'Strong'. Knee high immobilisation should be employed immediately while further diagnostic testing is performed to confirm or rule out the presence of the disease.

In summary, active CNO can be diagnosed when there are clinical signs of inflammation in combination with abnormalities on imaging. If such imaging is not immediately available, immediate immobilisation/offloading with a below knee-high offloading device should be initiated while awaiting further diagnostic testing (discussed in the next section of this guideline) in order to prevent further progression of the disease. Offloading will be discussed in more detail in the 'Treatment' section of this guideline. Thorough clinical examination, high index of suspicion, imaging, and prompt offloading are paramount to recognising and treating active CNO.

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?

Recommendations

6. Perform plain X-ray of the foot and ankle in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. Ideally, bilateral plain X-rays should be performed, if possible, for comparison purposes. Best Practice Statement.
7. Perform X-rays that include the anteroposterior (AP), medial oblique, and lateral projections in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. The ankle and foot views should include the AP, mortise, and lateral projections. Ideally, standing (also known as 'weight- bearing') radiographs should be performed. If a patient is not able to bear weight on their feet, non-weight-bearing radiographs are an alternative, but may not demonstrate malalignments that are more apparent in the standing position. Best Practice Statement.
8. Perform Magnetic Resonance Imaging in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with normal appearance of the plain X-rays to diagnose or exclude the disease and its activity (Strong; Moderate).
9. If Magnetic Resonance Imaging is unavailable or is contra-indicated in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy, consider a nuclear imaging scan (scintigraphy), CT (computed tomography) scan, or SPECT-CT (Single Photon Emission Computerised Tomography) to support the diagnosis of active Charcot neuro-osteoarthropathy (Conditional; Low).

Rationale

In a person with suspected active CNO, plain X-rays of the foot and ankle should be obtained in order to diagnose the disease as the involvement of bones and/or joints play a central role. Weight-bearing radiographs are preferred, as they may detect dynamic abnormalities, such as joint mal-alignment, joint subluxation, and/or fracture displacement that may not be apparent on non-weight-bearing radiographs.[50] The three standard foot views (antero-posterior (AP), medial oblique, and lateral) and three standard ankle views (AP, mortise and lateral) provide sufficient radiographic evaluation of the osseous anatomy. For an accurate diagnosis, all potentially involved bone and joint structures should be adequately visualised using such a standardised approach. Based on these arguments, we made the two Best Practice Statements as formulated above. We do acknowledge that weight-bearing radiographs are sometimes not feasible due to limited mobility of the person involved or when the risk of further displacement of joints and/or bones is

probably excessive. In such circumstances, non-weight bearing plain X-rays can be obtained. Table 1 describes the typical imaging abnormalities that can be observed in active CNO on plain X-ray (Figure 1).

As has been shown in several studies, patients with suspected active CNO based on the clinical grounds (i.e. warm, swollen foot) can exhibit normal appearing plain X-rays, however with clear abnormalities on more advanced imaging confirming involvement of bones and/or joints of the affected feet.[37,51–53] These patients can subsequently progress to overt fractures[37] and progressive malalignments. Such abnormalities, therefore, are also sufficient to support the diagnosis of active CNO, after the exclusion of other causes of acute bone and/or joint injury. MRI is most studied in this domain,[37,51–54] and this advanced imaging technique is not only able to detect bone/joint abnormalities but also signs of inflammation and/or remission in and around bones and joints with good to excellent sensitivity and specificity in various disease states.[55] In our systematic review, MRI demonstrated high sensitivity but unknown specificity for the diagnosis of active CNO in individuals with clinical suspicion, intact skin, and normal radiographs although these studies were from one centre only.[37,51–53] Because of lack of data on the specificity of MRI to identify active CNO, but high values of specificity reported in other inflammatory conditions to detect inflammation, we rated the certainty of evidence as moderate. Due to the fact that not diagnosing and treating the disease can have deleterious consequences, we made a Strong recommendation to perform MRI in the event of normal plain X-rays and clinical suspicion of active CNO, in order to diagnose or exclude the disease.

TABLE 1 Key findings on radiographs, CT and MRI for active Charcot neuro-osteoarthropathy and Charcot neuro-osteoarthropathy in remission.

Modality	Active stage of CNO	Remission stage of CNO
Radiographs (XR)	• Diffuse soft tissue swelling • Joint effusion (s) • Reduced bone density • Cortical erosions • Fracture (s) • Fracture fragments/Calcific debris in soft tissues • Radio-opaque foreign body may be seen • Subluxation or dislocation (s) • Disorganisation of articulation (s) • Background XR findings of remission stage may be present	• Decreased or resolved soft tissue swelling • Improved/Restored/Increased bone density • Cortical and subcortical cysts • Osteosclerosis and bony consolidation • Calcific debris in soft tissues • Disorganisation of articulation (s) • Radio-opaque foreign body may be seen
CT scan	• Above described XR findings are more conspicuous • Joint effusions of small joints better seen • Fluid collection or tenosynovitis may be seen at the areas of bony destruction • Skin ulceration may be present • Plantar muscle fatty atrophy may be seen. • Dual-energy CT shows bone marrow oedema at CNA sites	• Above described XR findings are more conspicuous • Decreased joint effusion, tenosynovitis, or fluid collection • Plantar muscle fatty atrophy may be seen.
MRI	• Diffuse soft tissue swelling and fascial oedema • Denervation oedema-like signal on fluid-sensitive imaging sequences (T2W or STIR- short tau inversion recovery) and/or fatty replacement on T1W imaging of foot muscles • Increased signal and/or thickening of the posterior tibial nerve • Joint effusion (s) and tenosynovitis • Increased fatty marrow related to osteopenia • Cortical erosions as loss of T1W signal intensity and bone marrow oedema on fluid-sensitive sequences. Overlying cartilage erosions are common • Multiple (>2) hindfoot bones are typically involved • Subchondral fracture (as subchondral dark signal in a cloud of oedema on fluid sensitive T2W or STIR sequence) and other cortical fracture (s) • Fracture fragments • Subluxation or dislocation (s) • Disorganisation of articulation (s) • Skin ulcer or devitalised/gangrenous soft tissue better seen as non-enhancing soft tissue on contrast-enhanced MRI • Increased soft tissue and bone perfusion on dynamic contrast enhanced MRI • Background MRI findings of remission stage may be present	• Decreased or resolved soft tissue swelling • Decreased bone marrow oedema • Cortical and subcortical cysts • Better defined bony hypointense cortical margins • Calcific debris/chronic fracture fragments/necrotic-sclerotic bones as hypointense signal on all sequences • Disorganisation of articulation (s) • Spring ligament/plantar fascial/tibialis posterior tears, etc. • Increased signal and/or thickening of the posterior tibial nerve • Decreased soft tissue and bone perfusion on dynamic contrast enhanced MRI

Abbreviations: CNA, Charcot neuroarthropathy; STIR, short-TI Inversion Recovery; XR, xray.

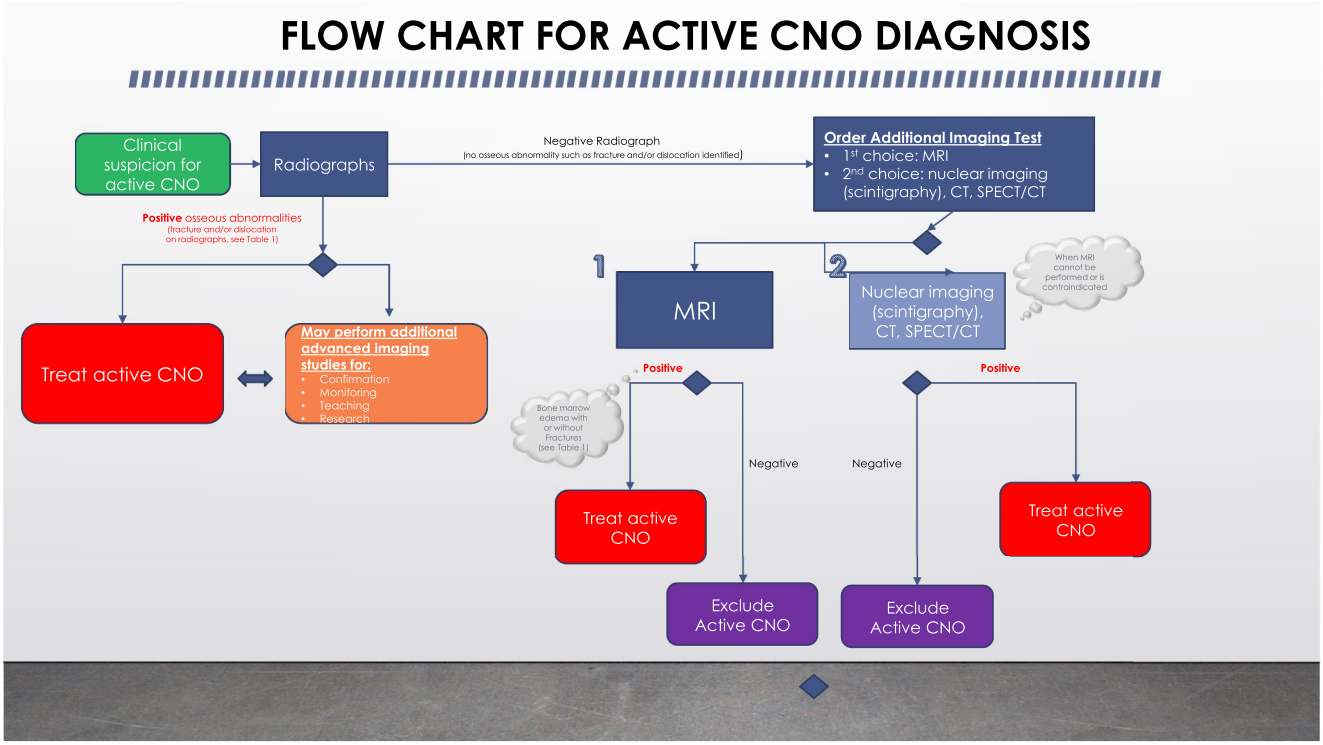

FIGURE 1 Flow chart for diagnosis of active Charcot neuro-osteoarthropathy.

There are several clinical scenarios where MRI cannot be performed: it can be contraindicated (for example, a patient with an MRI-unsafe pacemaker or MRI being not available at the medical facility) or too costly for the patient with suspected active CNO and negative X-rays. In these situations, other advanced imaging modalities can be performed as feasible, such as a nuclear imaging scan (scintigraphy) or CT scan to support the diagnosis of active CNO.[56–58] In our systematic review, we identified three studies that assessed the findings of nuclear imaging in persons with suspected active CNO and intact skin.[56–58] In a retrospective interrupted time-series non-controlled cohort study, 99 mTc-hydroxymethylene diphosphate three-phase bone scintigraphy was performed in 148 patients with suspected active CNO and had high (89%) sensitivity but limited (58%) specificity.[57] A non-controlled study of 18F-FDG positron emission tomography (PET)/CT scanning in 25 patients with suspected active CNO demonstrated increased uptake in all patients with suspected active CNO.[58] We recognise the limited specificity does not confirm the presence or absence of the diagnosis of active CNO, however a negative bone scan, SPECT/CT or negative PET/CT would be strong evidence against the diagnosis of active CNO. The diagnostic accuracy of MRI has not been compared with nuclear medicine scintigraphy. We have chosen MRI as the first option after plain X-ray, as this imaging technique provides more information to support or exclude the diagnosis of CNO due to better soft tissue contrast, and probably has, in our opinion, better specificity.

When MRI is not available or not possible, we recommend other modalities, such as nuclear imaging scan or CT scan for further assessment. Nuclear imaging combined with CT (SPECT-CT) may provide more utility than either nuclear imaging or CT alone due to improved spatial and contrast resolution, although this has not been studied specifically in active CNO in a case-controlled design. If the diagnosis is missed because these alternative investigations are not performed and the active CNO is not treated adequately, there is a substantial chance that the disease will progress, leading to worsening deformity and increased morbidity. When active CNO is considered and the radiographs are normal, immobilisation/off-loading with preferably, non-removable below knee-high offloading device should be initiated immediately while advanced imaging results are pending. If these investigations cannot be performed, the patient should be treated as having the active disease until all symptoms have disappeared, but such a pragmatic approach may also result in unnecessary treatment and increased financial and non-financial burden in persons not having the disease.

Possible adverse effects of X-rays and CT are increased exposure to ionising radiation for the individual and the environment. CT scanning involves more exposure than radiographs and increased/repetitive exposure over time can increase the risk of long-term health effects. However, extremities are relatively radioresistant.[59–61] Weight-bearing CT is also available to detect malalignment of the foot and ankle, although not as readily available as conventional CT. Nuclear imaging utilising radioactive tracers has minimal risks and these risks would be limited to very rare allergic reactions and radiation exposure risk from small doses of ionising radiation. The disadvantages of advanced imaging are that they are less readily

available, incur higher costs compared to the standard radiographs, and can lead to a substantial financial burden for affected individuals and the health care system. However, advanced imaging including MRI has become more affordable and accessible recently, especially in high income countries, resulting in more accuracy in diagnosing and excluding CNO. Although costs-effectiveness data are lacking, it is therefore recommended that these imaging techniques, in particular MRI as the first step, should be considered when plain radiographs are normal.

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?

Recommendation

10. We suggest not using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count, alkaline phosphatase, or other blood tests in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin to diagnose or exclude the disease (Conditional; Low).

Rationale

Blood tests such as measurements of serum inflammatory markers (CRP, ESR and WBC) or alkaline phosphatase are often obtained in the setting of active CNO. Our systematic review identified five observational studies that measured either CRP, ESR, and/or alkaline phosphatase in patients with active CNO and intact skin.[22] Five of the studies that we identified measured CRP,[62–66] three measured ESR,[63,64,66] three measured white blood cell count (WBC)[63,65,66] and three measured alkaline phosphatase.[62,63,67] All studies were of low quality and at high risk of bias.

In the studies included for review, serum CRP ranged from normal to as high as 324% above the reference range (<5 mg/L).[62–66] ESR in active CNO patients with intact skin ranged from a mild increase (5%) to as high as 350% above the reference range (<20 mm/h).[63,64,66] WBC was reported normal[63,65] in two studies (reference range $<10^9$/L) and mildly elevated (10% above reference range) in one study.[66] Serum alkaline phosphate was found to be normal in active CNO in two studies.[63,67] Serum bone-specific alkaline phosphatase was 21% higher in patients with active CNO compared to control participants with diabetes mellitus however this elevation was not statistically significant.[62]

In conclusion, we did not identify evidence to support the use of CRP, ESR, WBC or alkaline phosphatase in diagnosing active CNO. Our conclusion was based on the wide range of values reported in these studies with high imprecision. The quality of evidence was low and for this reason we graded the recommendation as 'conditional'. Although the aforementioned systemic inflammatory markers can be elevated in active CNO, probably due to the underlying sterile inflammation in the foot, other diagnoses should also be considered.[68]

6.2 | Identification of remission

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

Recommendations

11. Consider the measurement of skin temperature of the affected and unaffected limb with serial examinations to monitor disease activity in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin (Conditional, Low).
12. We suggest not using soft tissue oedema alone to determine when active Charcot neuro-osteoarthropathy is in remission (Conditional; Low).
13. We suggest that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that active Charcot neuro-osteoarthropathy is in remission (Conditional; Low).
14. We suggest that the frequency of appointments for assessing disease activity in active Charcot neuro-osteoarthropathy should depend on specific factors such as fluctuation in oedema volume, co-morbidities, the risks associated with treatment and recovery, access to assistance with home treatment needs, and a person's progress and recovery (Conditional; Low).

Rationale

Our systematic review identified five studies that evaluated different types of monitoring techniques to define remission of active CNO.[49,54,69–71] All were observational studies with high risk of bias. Two studies reported the predictive value of using infrared thermometry to monitor and identify remission based on clinical grounds, following the same protocol but using different thermometry devices.[49,70] In one study, the site of maximum skin temperature difference between the affected and unaffected foot was found to correlate with the radiographic imaging at diagnoses in 92% of cases and during follow-up in 72% of cases.[49] Another prospective observational study provided a narrative report showing agreement between a temperature difference (4°F/2°C) and radiographic findings for identifying remission in active CNO.[70]

There were three studies that evaluated the use of MRI to identify remission in active CNO, and also reported that they assessed skin temperature.[54,69,71] The first study was an open label cohort study and compared 3-monthly dynamic MRI scans, with gadolinium contrast medium, with the clinical healing defined as the combination of a temperature difference <1°C and difference in the circumference at the midfoot and ankle level <1 cm (as measure of swelling).[69] The authors reported a 90% agreement between clinical and MRI findings. However, in 23% of patients clinical healing (absence of inflammation) preceded MRI healing by 3–6 months. The authors did not analyse the results of skin temperature separately.

Unfortunately, the second and third MRI studies could not provide any useful evidence to help answer this clinical question and support subsequent recommendations.[54,71]

We recommend that providers use infrared thermometry to monitor active CNO and identify remission based on the balance of risks and harms, confidence in the results, feasibility, acceptability, and equity. The measurement of temperature is of no harm and no risk to the patient and is a safe, low/no cost examination tool that is relatively easy to perform. The higher the temperature difference between the affected and unaffected foot the greater the likelihood of ongoing disease activity and conversely, the lower the temperature difference the greater the likelihood that the CNO is going into remission. At this time, there is insufficient evidence to recommend a specific temperature cut-off at which point remission occurs. As such we recommend that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that the active CNO is in remission. Both the provider and patient must recognise that the transition from active CNO to remission may take many months. The advantages of infrared skin temperature measurement over radiological investigations to monitor active CNO are that it is cheaper, quicker, more readily available, non-invasive, and there are no safety considerations. The protocols for temperature measurements in these studies allowed for an acclimatisation period of 15 min, which is time consuming.

There is evidence that when the limb with active CNO is offloaded, the amount of leg/foot oedema reduces. In our systematic review we identified two studies which compared objective assessment of soft tissue oedema to radiological findings and in another study soft tissue oedema was assessed subjectively.[54,69,71] From these studies it was not possible to identify whether there is a relationship between clinical assessment of oedema and radiological findings to ascertain remission in active CNO. Based on expert opinion, we recommend that subjective or objective assessment of soft tissue oedema may contribute to a complete patient assessment to identify remission in active CNO, and we graded the recommendation as 'Conditional'. There is no evidence to support a recommendation on a specific protocol for measuring soft tissue oedema in active CNO. However, we would advise that a standardised approach to evaluating soft tissue oedema be used to allow for more accurate comparison over time. It should be noted that the potential limitations of assessing soft tissue oedema are similar to those for temperature measurement, with the presence of bilateral foot disease, absence of contralateral limb or concurrent foot ulceration and/or infection affecting the usability and interpretation of any results. We acknowledge that remission is defined as the absence of clinical signs of inflammation and is based on clinical judgement because we cannot give absolute values to define the absence of inflammation. We recognise that in certain cases mild signs of inflammation such as oedema can persist despite radiographic consolidation.

There is no evidence to support a recommendation on the frequency of infrared thermometry or other clinical measurements to monitor the disease activity of CNO. To reflect clinical practice, we suggest that temperatures are assessed at serial visits, to coincide with appointments for cast change, or to have offloading devices checked. Usually, a shorter period between appointments is necessary in the early phase of the disease as due to the reduction of oedema, the offloading device needs to be modified. Weekly clinical evaluations may be required when oedema reduction is rapid and frequent TCC changes are needed. As signs and symptoms stabilise, time between clinical evaluations can be increased up to 3–5 weeks. We suggest close monitoring due to the burdensome and costly effects of unnecessary treatment that would result in missing harmful effects (e.g. ulcers) that may occur if an individual in remission is not closely monitored.

We encountered two main difficulties when developing our recommendations. Firstly, the lack of a standardised clinical or radiological definition of remission of the disease, and secondly, there is currently no agreed 'gold standard' test to ascertain the remission of active CNO. None of the studies we identified in our systematic review reported the sensitivity or specificity of using skin foot temperature to identify remission, either in isolation or compared to imaging.[22] For these reasons we graded the strength of our recommendations as 'Conditional'.

Uncertainty remains about the effectiveness of temperature assessment to monitor active CNO, and whether the different devices and protocols used influence time to remission. Different cut-off points have been used, 4°F (which is 2.2°C), 2°C, and 1°C.[49,70] There is a need for high-quality studies to assess the diagnostic accuracy of temperature assessment to determine remission in CNO. Until a 'gold standard' test for identifying active CNO has been identified and validated we recommend that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that the active CNO is in remission. We acknowledge that occasionally individuals will present in remission who have not had previous treatment.

6.3 | Treatment

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

Recommendations

15. Use a non-removable knee-high device to immobilise and offload the foot to promote the remission of the disease, and prevention or progression of deformity in a person with active Charcot neuro-osteoarthropathy and intact skin (Strong; Low).
16. Consider using a total contact cast in the treatment of active Charcot neuro-osteoarthropathy with intact skin in a person with diabetes mellitus. A knee-high walker rendered non-

removable can be considered as a second choice in order to immobilise and offload the foot (Conditional; Low).

17. A removable knee-high device worn at all times can be considered as the third treatment choice in a person with diabetes mellitus, active Charcot neuro-osteoarthropathy and intact skin of the foot for whom a non-removable knee-high offloading device is contraindicated or not tolerated (Conditional; Low).
18. We suggest not to use a below the ankle offloading device (e.g. surgical shoe, postoperative sandal, custom moulded shoe, or slipper cast) in the treatment of active Charcot neuro-osteoarthropathy and intact skin, given the inadequate immobilisation of the diseased bone and joints, and limited off-loading capacity (Conditional; Low).
19. Treatment with a knee-high offloading device should be considered as soon as possible once the diagnosis of active Charcot neuro-osteoarthropathy is considered (Strong; Low).
20. In a person with active Charcot neuro-osteoarthropathy who is being treated with a knee-high device, we suggest using assistive devices to reduce weight-bearing on the affected limb (Conditional; Low).

Rationale

As discussed below, there are several strong arguments that the diseased, inflamed foot in active CNO should be immobilised and offloaded in a knee-high, non-removable, device. It is important to institute immobilisation even in the absence of fractures on plain radiographs, when other imaging techniques (such as MRI) suggest active CNO. This immobilisation should be started immediately once the diagnosis of active CNO is considered. Additional evidence provides guidance that a total contact cast (TCC) might be considered as first choice, and a knee-high walker that is made non-removable as second choice. Total contact casts are usually made of plaster of Paris or fibreglass that is in close contact with the entire foot and lower limb. Comparable offloading of the foot can be achieved by a prefabricated knee-high walker that immobilises the foot and can be rendered irremovable by applying a layer of cast or tie wrap around the device.[72] Both devices and their insoles should be applied in such a way that they accommodate any foot deformity safely and provide pressure redistribution in order to prevent subsequent ulceration. A removable knee-high device worn at all times with an appropriate foot-device interface to reduce peak pressure[23] can be considered as the as a third treatment choice in a person with diabetes mellitus and active CNO and intact skin of the foot for whom a non-removable knee-high offloading device is contraindicated or not tolerated. A possible benefit of a removable knee-high device is that it can be removed for bathing or examination of the skin. The main disadvantage and concern when using removable knee-high devices is the potential for non-adherence to the offloading/immobilisation treatment which may lead to development/progression of deformity and delayed time to remission.

As described in our systematic review, there is limited high-quality evidence on which to base our recommendations.[22] Our recommendations on offloading active CNO are based on a combination of the direct and indirect evidence from research where available, and expert opinion where no such evidence exists. The potential negative consequences of not initiating offloading as soon as possible once active CNO is suspected include progressive deformity and potential skin ulceration. Therefore, we made the recommendation of offloading once active CNO is suspected a 'Strong' recommendation. The rationale behind offloading the foot and leg in active CNO is that increased mechanical stress plays a central role in perpetuating the underlying inflammatory disease process, resulting in progressive bone destruction, development of fracture(s) and joint dislocation. Although individuals with active CNO can present with only one fracture on plain X-ray, more advanced techniques such as MRI, SPECT/CT and PET-CT usually show that multiple bones and joints in the foot and ankle are affected.[51,56,73] It is for this reason, that immobilisation and off-loading of the complete foot and ankle is indicated. Our recommendations are in line with other guidelines on the management of individuals with high-risk non-displaced foot fractures, irrespective of the presence of diabetes in order to optimise fracture healing, prevent malalignment, non-union and progressive dislocation.[74–76]

By using a knee-high device, plantar pressure and ground reactive forces are redistributed more proximally serving to offload the inflamed foot.[77] Knee high devices immobilise the ankle joint and minimise the deforming effects of the lower limb muscles on the joints in the foot and ankle. There is evidence from clinical and biomedical/laboratory research that immobilisation and offloading usually results in a decrease in the clinical signs of inflammation as well as reduction in circulating pro-inflammatory markers over time.[62,64] Although immobilisation and offloading of the complete foot and ankle are indicated, patients can have difficulties in accepting and using knee-high offloading devices as they can have little or no pain, and such devices can have negative effects on mobility, autonomy, driving, self-esteem and perception by others.[78] Moreover, if not applied correctly in persons with loss of protective sensation, these devices can result in the development of skin breakdown anywhere distal to the knee. A new cast associated blister or ulcer was reported in 14% of people with diabetes who were treated with a total contact cast in a recent study.[79] The patient should therefore be well informed about the risks of inadequate treatment, its benefits and harms and should be supported in integrating this treatment in their daily life.

In our systematic review, we could not identify intervention studies comparing the efficacy of a non-removable with a removable off-loading device. However, in the nationwide UK survey of 219 people with active CNO, the median time to remission, defined as the patient being mobile in (therapeutic) footwear, was three months longer in those treated with a removable device compared to those who had a non-removable device.[80] Likewise, studies in patients with diabetes and a neuropathic foot ulcer have shown that despite intensive education, they do not wear removable offloading devices as advised, and this can contribute to delayed ulcer healing.[55] Due to the absence of pain, people with active CNO may continue to walk on the diseased foot and they sometimes only seek medical help when

their foot becomes so deformed or swollen that it does not fit in the shoe anymore.[34] We could not identify studies on patients' preference in active CNO but one study reported that in patients with a diabetic foot ulcer, patients preferred a non-removable device once the benefits were clearly explained.[66] People may therefore initially prefer a prefabricated removable device because they can take it off in situations like going to bed, driving a car, or bathing, but they should be informed about the greater expected benefit of a non-removable knee-high device in preventing deformity, shorter treatment period with consequent lower short- and long-term health care costs.[55,61] For these reasons, we graded the strength of the recommendation on the use a non-removable knee-high device, either a TCC or a prefabricated walker made non-removable, as 'strong'. However, we acknowledge that for this specific disease state evidence based on clinical trials is lacking.

The affected leg can be immobilised and offloaded either by a TCC or by a prefabricated knee-high walker.[23] The majority of studies we included in our systematic review used TCCs as the preferred method of offloading.[22] We could not find any studies that addressed our clinical question and compared treatment with TCC to prefabricated knee-high walkers on the outcome of active CNO. As discussed earlier the aim of treatment is primarily to immobilise the joints in the foot and secondly, to offload the foot by redistributing plantar pressure from ground reactive forces. It is this requirement for immobilisation that has led to the recommendation based on the expert opinion of the group that TCCs might be preferable to prefabricated walkers. The advantage of the TCC is that there is probably better immobilisation of the ankle. For instance in patients with severe ankle sprain a TCC had better overall results than a prefabricated walker.[81] In addition, a TCC is applied to fit the person's limb, and each TCC is customised to accommodate deformity or significant oedema. The disadvantage of a TCC is that is needs renewal at each visit (unless it is made removable but that can result in less optimal immobilisation), is associated with higher costs, and requires expertise and therefore has a greater negative impact on equity. It is likely that patients value both TCC and knee-high walkers as equally unpleasant interventions, although we could not identify in our systematic review studies on the impact of quality of life of the different treatment modalities. In summary, there is some indirect evidence supporting the use of TCC as first choice in the treatment of active CNO and a non-removable walker as second choice. In particular when costs or equity play an important role or specific expertise is lacking walkers, made non-removable, can be preferable, but future studies are needed in this area. Therefore, we graded the strength of our recommendation as 'conditional'.

Treatment with a non-removable knee-high off-loading device should be started immediately when active CNO is suspected, and continued unless an alternative diagnosis is made, in order to prevent the development of deformity.[82] The importance of early immobilisation and reduced weight-bearing on the diseased foot is highlighted by two studies of Chantelau and co-workers. In these retrospective observational studies with a high risk of bias, these authors reported that patients diagnosed with Charcot stage 0 who were treated early (i.e. those without fracture on plain X-ray before TCC treatment) rarely developed a subsequent deformity in marked contrast to those diagnosed and treated in stage 1 (i.e. those with a fracture on plain X-ray).[37] In the second study, the time of unrestrained weight-bearing as well as the weight- bearing intensity before treatment was initiated was associated with the development of deformity in patients with active CNO.[83] Although evidence based on clinical trials is lacking and we have no information on aspects such as cost-effectiveness and equity, the guideline committee concluded that the immobilisation of the affected leg should be started at the moment active CNO is considered, given the potentially devastating consequences of untreated CNO.

Persons with active CNO should be informed that it can take many months before the disease goes into remission. Our experience suggests that offloading be continued for four to 6 weeks after the clinical signs of active CNO have resolved and the patient is diagnosed as in remission. Long-term treatment with a non-removable knee-high device is associated with the risk of complications and adverse effects. Only a few studies identified in our systematic review reported such events. The most important complications being the development of foot ulcers that sometimes resulted in amputation in two studies,[84,85] skin lesions from injury during the removal of the cast, and pain[86]. Other possible adverse effects include muscle weakness and atrophy, falls and musculoskeletal knee or hip complaints because of the acquired limb-length discrepancy when wearing the device, as described in our ulcer offloading guideline.[72] One may consider a shoe raise for the contralateral limb to minimise this acquired limb-length discrepancy. The long-term loss of mobility can have major negative consequences on people's psychological health, physical health and socio-economic well-being due to the increased risk of social isolation and loss of work. Furthermore, loss of mobility can have negative effects on glucose control and other cardiovascular risk factors.[87]

We suggest not to use below the ankle devices in the management of active CNO. We could not identify studies that evaluated the therapeutic value of the ankle devices to treat active CNO and therefore made a 'conditional' recommendation. However, there is indirect evidence from studies in people with diabetes related foot ulceration that ankle high devices do not immobilise and offload the foot as effectively as knee-high devices.[72]

To achieve reduced weight- bearing we suggest using assistive devices to reduce (1) pressure on the affected limb, (2) risk of falls, (3) time to remission, and (4) the risk of musculoskeletal injury and pain in the affected or contralateral limb. The recommendation on the use of, preferably bilateral, crutches in addition to treatment with a knee-high device is based on one retrospective study in which patients were instructed in partial weightbearing of the casted extremity by using bilateral axillary crutches or walker.[88] Seventy-two percent of the patients did not adhere to these instructions as judged by their treating orthopaedic surgeon and in these patients the average time to healing was 34 days longer compared to those who did comply.[88] Secondly, continued walking on the extremity in a knee-high device can result in musculoskeletal complications and pain in the contralateral extremity, as described above. The balance of effects

regarding weight-bearing status probably favours reduced weight-bearing compared to unrestricted or non-weight-bearing, however, the quality of evidence is very low. Based on these arguments we suggest considering partial weight- bearing with the use of crutches, walkers, rolling crutch walkers or other devices, and this choice should be adapted to the patient's living conditions, mobility and motivation of the patient.

Although our recommendations are in line with other guidelines,[39,82,89] the evidence from observational studies highlight that the implementation of our recommendations may be a challenge as many people seem to receive sub-optimal treatment with potentially poorer outcomes. In the nationwide UK survey from 2005 to 2007 approximately one third of all patients with active CNO were not treated with a non-removable offloading lower leg device.[80] Comparable results were obtained in a 1999 survey conducted under members of the Diabetes Committee of the American Orthopaedic Foot and Ankle Society, as approximately half of the patients with a history of a Charcot foot had initially not been treated with a TCC.[90] This variability in treatment is likely to be associated with the absence of treatment guidelines accepted by all the different disciplines involved in treating these patients, the lack of evidence based on clinical trials, lack of knowledge, skills and resources to apply TCCs as well as patient-related factors and reimbursement, and perhaps clinical inertia. The phenomenon of clinical inertia is defined as the failure to start a therapy or its intensification/non-intensification when appropriate, in patients with a disease such as active CNO.[91]

Treating patients with active CNO as well as the application and use of TCCs and non-removable knee-high devices requires specific training, skills and experience. We suggest that the healthcare professionals treating these patients should have access to high-quality training according to national or regional standards. To facilitate implementation, offloading recommendations should be culturally appropriate, account for socioeconomic status, align with a patient's health literacy as well as personal circumstances, and should be part of a shared decision-making process. When these factors are taken into account, this will probably enhance their acceptability and feasibility. It is therefore not possible to provide globally applicable recommendations on the best form of offloading given the diversity of contexts and situations in which people present with active CNO. The financial resources required for total contact casting and knee-high removable offloading device can be challenging to provide for healthcare providers, and for people who are required to self-fund their own healthcare.

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?

Recommendation

21. Do not use alendronate, pamidronate, zoledronate, calcitonin, parathyroid hormone, or methylprednisolone as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin (Strong; Moderate).
22. We suggest not to use denosumab as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin (Conditional; Low).
23. We suggest evaluating the need for vitamin D and calcium supplementation in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin during the phase of fracture healing, in doses according to (inter)national guidelines on supplementation in persons at risk of vitamin D deficiency and/or those with insufficient calcium intake (Conditional, Low).

Rationale

The pathophysiology of CNO is associated with localised increased bone resorption, osteopenia, and osteoporosis, all of which can lead to bone weakness. Therefore, the use of several pharmacological therapies to treat CNO has focused on restoring the balance between bone formation and resorption. The aim of treatment is to reduce time to remission and/or help to prevent the development or worsening of foot deformities that are already present at the first clinical presentation.

Our systematic review identified eight studies, on several different pharmacological interventions used in the management of active CNO.[22] There were seven randomised controlled trials (RCTs) and one cohort study. The studies could be subdivided firstly into therapies that potentially inhibit bone resorption in the early inflammatory phase of the disease, bisphosphonates (alendronate, pamidronate, zoledronate), calcitonin and denosumab; secondly into agents that could stimulate bone formation, parathyroid hormone and finally, anti-inflammatory therapies, methylprednisolone. Most studies reported time to remission and the development of foot deformity was an outcome in two of the studies.

Five of the eight included studies investigated the potential beneficial effect of bisphosphonates in the treatment of active CNO, as described in our systematic review.[22] These drugs have been used in the treatment of osteoporosis for many years and have a well-known risk profile. Most of the bisphosphonate studies had a high risk of bias with the exception of the high-quality RCT, from Jude et al.,[92] on the efficacy of intravenous pamidronate versus placebo. None of these studies reported an improvement in time to remission[92–95] and treatment with zoledronate was associated with a longer time to remission.[94] Two of these studies reported that treatment with pamidronate or alendronate may be associated with a reduction in pain.[92,95] Several of the aforementioned studies reported improvements in biomarkers of bone resorption and/or bone formation, but the clinical significance of these observations is unclear and could also be related to systemic effects of the drugs.

One RCT of intranasal calcitonin, with a high risk of bias, did not observe any effect on time to remission during 6 months of follow-up.[96] Daily subcutaneous PTH was evaluated in one RCT with a low

risk of bias, without any beneficial effect on time to remission, fracture healing or prevention/progression of foot deformity.[97] A non-blinded RCT with a high risk of bias, reported that treatment with methylprednisolone was associated with a longer time to remission compared to both zoledronate and placebo treatment.[98] Given the lack of evidence for their efficacy, potential side effects, resources required and impact on equity, we recommend not to use alendronate, pamidronate, zoledronate, methylprednisolone, calcitonin or PTH as treatment for active CNO in people with diabetes mellitus.

The final study included in the systematic review was a cohort study at high risk of bias with historical controls, some of whom were treated with bisphosphonates. This study reported that a single injection of denosumab was associated with a faster time to remission, the duration of TCC treatment was approximately 1 ½ month shorter, and time to fracture healing on plain X-ray was shortened by approximately 2 months with less malalignment.[99] The effect on the prevention of deformities could not be assessed due to the small number of events. Given the lack of clinical trials, the costs, and potential adverse effects, there was at the time of writing these guidelines insufficient evidence to suggest the use of denosumab in the treatment of active CNO. We made a 'conditional' recommendation not to use this therapy based on the limited quality and inconsistency of the evidence reported and the results of randomised clinical trials need to be awaited.

Vitamin D and calcium play an important role in skeletal health and bone repair, and persons with type 2 diabetes have more frequently low vitamin D levels[100] as also observed in patients with active CNO.[101] We could not identify intervention studies on possible beneficial effects of vitamin D and calcium supplementation in active CNO. Also, indirect evidence to support such supplementation is poor as studies in traumatic or fragility fractures are scarce.[102] We have therefore no information on the impact of low Vitamin D levels or poor calcium intake on the course of active CNO. However, persons with active CNO can be at risk of low vitamin D levels, due to factors as type 2 diabetes, obesity, renal disease, and their older age. It is likely that key stakeholders would find calcium and vitamin D supplementation acceptable and feasible given their importance in bone healing. Therefore, given their importance for bone repair, the lack of major side effects, and the relative low costs, we suggest for pragmatic reasons to evaluate the need for vitamin D and calcium supplementation in persons with active CNO. When treatment is started, the doses of vitamin D and calcium should be prescribed according to (inter)national guidelines on supplementation in persons with – or at risk of – vitamin D deficiency and/or insufficient calcium intake.

In summary, based on indirect evidence we suggest considering vitamin D and calcium supplementation during treatment of active CNO. There is no evidence to support the use of any other pharmaceutical interventions, as such treatment will be associated with additional costs and potential harmful effects in this specific patient population. Potential harmful effects include impairment of bone healing and iatrogenic fractures.

Clinical question: In a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin, is reconstructive surgery associated with shorter time to remission, prevention of deformity development, and prevention of deformity progression compared to no surgery?

Recommendation

24. In a person with active Charcot neuro-osteoarthropathy and intact skin, and with instability of foot and ankle joints, and/or deformity with a high-risk of developing ulcer in the offloading device, or pain that cannot be sufficiently stabilised in a Total Contact Cast or a non-removable knee-high device, we suggest that surgical intervention should be considered (Conditional; Low)

Rationale

Historically, surgical reconstruction for active CNO has not been recommended largely due to concerns about performing surgery on an acutely inflamed foot. Our systematic review did not identify any prospective, randomised outcome studies comparing surgical versus non-surgical treatment during active CNO.[22] We identified one non-controlled retrospective study that evaluated the outcomes of patients with active CNO and intact skin who underwent primary realignment arthrodesis.[103] This study was limited to the surgical treatment of only 14 patients with active CNO localised to the tarsometatarsal joints, and these findings cannot be extrapolated to more proximal involvement such as the transverse tarsal joint, the subtalar joint, or the ankle joint.

The indications for surgical intervention during active CNO include deformities that result in impending skin ulceration, severe instability, intractable pain, or the inability to immobilise the foot in a cast or non-removable knee high device.[39] As discussed previously, the deformity associated with impending ulceration can lead to catastrophic outcomes, increasing the risk of major amputation by a factor of six to 12 fold.[10,11] Our recommendation to perform early surgical intervention during active CNO in specific subgroups is consistent with guidelines on the management of foot and ankle fractures in patients irrespective of diabetes status.

Based on clinical experience, proximal deformities of the hindfoot and ankle can be especially difficult to manage with TCCs or knee-high non-removable devices due to deformity in the coronal plane. Varus and valgus deformities of the ankle and hindfoot are poorly tolerated because of the subcutaneous nature of the medial and lateral malleoli. Consequently, skin breakdown and ulceration at the level of the medial and lateral malleoli can lead to osteomyelitis. A previous consensus statement recommended consideration of primary arthrodesis for active CNO of the ankle with severe deformity.[39]

Reconstructive surgery for CNO includes realignment arthrodesis, tendon lengthening, tendon transfer or partial ostectomy of a prominent bone (exostectomy). Surgical intervention in

CNO is associated with high complication rates and the risk benefit ratio needs to be considered when intervening surgically. A large database study compared outcomes of ankle fusion in a matched cohort of patients with diabetes and CNO (n = 3815) and patients with diabetes but without CNO (n = 3815).[104] Significantly higher rates of amputation, hardware removal, wound dehiscence, acute kidney injury, pneumonia, and surgical site infection, were observed in patients with diabetes and CNO compared patients with diabetes but without CNO. This study was not included in our systematic review as a main limitation of this database study was that the timing of surgery (active or remission stage) could not be determined, but these data highlight the risks of surgery in patients with CNO.

Although CNO reconstruction is associated with high upfront costs, reconstruction early in the disease process is, in our opinion, justified for patients who cannot be managed successfully with total contact casting or non-removable knee-high devices. Because CNO reconstruction is challenging and associated with relatively high complication rates, the goal is to pursue a cost-effective strategy of fixation and bone graft augmentation while still achieving a high rate of favourable outcomes. Our systematic review did not identify any studies which supported a superior or specific method of fixation, for example, internal versus external fixation, in treating active CNO with intact skin. The decision to use external or internal fixation is highly dependent on the surgeon's preference and experience.

The goal of surgical reconstruction for the patient with active CNO includes restoring a plantigrade foot that is less prone to ulceration because plantar pressure is redistributed throughout the foot. Complications of surgery include surgical site infection, wound dehiscence, non-union, hardware failure and need for further treatment. The level of evidence regarding surgery in active CNO is low, and the current evidence supports offloading with knee-high devices over surgery in the active CNO in patients with intact skin. Consequently, prior to performing surgery in active CNO, we recommend a period of non-surgical care to include immobilisation and oedema reduction to allow the inflammation to decrease prior to surgical intervention. The resources and costs associated with surgical intervention are higher than treating patients with offloading using a knee-high device. A Markov model-based study from Albright et al.[105] hypothesises that the most effective strategy for unstable midfoot CNO with intact skin favours surgical reconstruction despite its high upfront costs. To date this strategy has not been validated by any clinical series. As our recommendation is mainly based on indirect evidence and expert opinion, we graded it as 'conditional'. Given the uncertainties described above, the potential complications of surgery and the higher upfront costs, the potential beneficial effects should be carefully balanced with the risk of harm in an individualised manner. The final choice should be made by a well-informed patient as part of a shared decision-making process and the surgical reconstruction should be performed by a surgeon with sufficient expertise in foot surgery in high-risk patients with diabetes and CNO.

6.4 | Prevention of re-activation

Clinical question: In persons with diabetes mellitus and active Charcot neuro-osteoarthropathy 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?

Recommendation

25. Footwear and/or orthoses that best accommodate and support the shape of the foot/feet and ankle to help prevent re-activation of Charcot neuro-osteoarthropathy (CNO) are recommended in a person with diabetes mellitus, intact skin, treated for active CNO with an off-loading device and who is now in remission (Strong; Moderate).
26. When deformity and/or joint instability is present, in order to optimise the plantar pressure distribution, below the knee customised devices should be used for additional protection in a person with diabetes mellitus, intact skin, treated for active Charcot neuro-osteoarthropathy who is now in remission (Strong; Moderate).

Rationale

Based on our systematic review we did not identify any evidence that demonstrates that therapeutic footwear is superior to conventional footwear to prevent re-activation of active CNO.[22] Despite the paucity of data, our recommendation is to consider footwear that best accommodates and supports the shape of the foot/feet to help prevent re-activation of the active disease in people who are in remission. Being at increased risk of ulceration as a result of CNO related deformity, it is important that the person's footwear fits, protects, and accommodates the shape of their feet; this includes footwear having adequate length, width, and depth. When foot and/or ankle deformity is present, it becomes even more important to alter foot biomechanics and reduce plantar pressure on at-risk locations. This may require custom-made footwear, custom made orthoses or below knee braces. The second part of our recommendation, therefore, is that in people with diabetes mellitus and CNO who have been treated and are in remission is to consider prescription custom made orthotics to (redistribute) decrease plantar pressures. When custom made orthotics are prescribed, extra depth footwear should be used to accommodate the increased thickness of the orthotic.

Despite the lack of evidence, we strongly believe that therapeutic footwear would produce benefits in terms of reducing CNO re-activation and mechanical stress reduction. Our recommendation is consistent with IWGDF guidelines on the prevention of foot ulcers.[24] The IWGDF Risk Stratification System identifies persons with loss of protective sensation and foot deformity secondary to CNO at increased risk of ulcerations. Considering the potential benefit of additional ankle stability, we recommend removable knee-high offloading over ankle-high offloading in patients who require long-term ankle stability. We favour customised devices such as Charcot Restraint Orthotic Walker (CROW), contoured plastic ankle foot

orthosis (AFO), and the double upright metal AFO that is attached to the footwear to provide support.

The primary adverse effect of footwear, orthotics and braces in persons with diabetes-related neuropathy is an iatrogenic ulcer formation from ill-fitting shoes or orthotic devices. Because persons with loss of protective sensation cannot adequately judge footwear fit, footwear and braces should be evaluated by appropriately trained professionals. The benefits of prescriptive footwear, orthotics, and braces outweigh the low incidence of ulcer formation, and for further information we refer to the IWGDF guidelines on the prevention of foot ulcers.[24]

Although evidence is lacking, we suggest that the affected foot should be gradually transitioned to the advised footwear and that in this phase ambulation should slowly increase. Abrupt re-loading of the foot may reactivate the CNO. In addition, probably due to the inflammatory process and the long-term immobilisation, the foot skeleton can become osteoporotic.[106,107] Rapid and accelerated transition into weight-bearing activities with increased loading of the foot may, in our clinical experience, may result in osteoporotic fractures.

6.5 | Future research

As discussed in this guideline and in our systematic review[22] there is an urgent need for further clinical research in active CNO. Our systematic review identified multiple areas where high-quality evidence is lacking. Although CNO is considered a 'rare disease,' the number of actual individuals with this disease is likely higher than we think due to misdiagnosis and lack of awareness.

Based on the findings of our systematic review[22] and subsequent guideline development, we consider the following topics to be key in future research:

Diagnosis and monitoring: One of the major items that needs to be addressed is the development of well-defined and validated, objective and reproducible criteria to diagnose active CNO, to monitor disease activity, and to determine remission. There are no studies that have demonstrated the accuracy of foot skin temperature measurement to diagnose active disease or determine the presence of remission. In particular, the diagnostic accuracy of the ≤2°C foot skin temperature measurement 'cutoff', that is frequently used, has not been demonstrated in a clinical study and warrants further research. Also, we do not know which specific infrared thermometry device or protocol provides the most accurate method for measuring foot skin temperature. Future studies assessing the use of home monitoring with infrared thermometry devices to monitor disease activity would be beneficial. This would allow the patient to liaise with the clinic without the need to attend clinic appointments as frequently and be able to identify changes in their foot condition rapidly and seek advice.

Further studies on the monitoring of disease activity from an imaging standpoint are also needed. Although MRI can detect active CNO with high sensitivity, the abnormalities on MRI can persist after the clinical active CNO symptoms have resolved.

Offloading: Although TCC is accepted as the 'gold standard' method by many authors for offloading in patients with active CNO, further studies may help demonstrate which offloading modality is most effective to achieve remission, acceptable to people with CNO given socio-economic factors, and most cost-effective.

Weight-bearing: Studies are needed to determine whether or not weight -bearing in an offloading device can negatively impact time to remission and development/progression of an existing deformity.

Treatment: We suggest that the potential efficacy of denosumab and tumour necrosis factor inhibitors could be studied in future RCTs to assess the benefits, risks and cost-effectiveness of these potentially useful treatments.

Surgical intervention: Studies are necessary to determine whether early surgical intervention during the active CNO phase can improve outcomes (prevention of deformity, time to remission) compared to standard offloading.

Risk factors/genetics: Further work to identify risk factors associated with the development of active CNO is needed. Not all individuals with diabetes mellitus and neuropathy develop CNO therefore identifying risk factors/genetic markers/a screening tool to assess the level of risk of the development of active CNO would be of significant importance in regard to prevention of complications related to this disease.

In general, the quality of studies related to diagnosis and intervention in active CNO and the way they were reported was, with few exceptions, poor. They were generally underpowered, non-blinded, and did not include relevant clinical outcomes such as prevention of deformity. In order to move the field forward with better quality studies, consensus must be reached on appropriate participant selection/characteristics, how the disease is monitored, how objective endpoints should be defined, which side-effects should be systematically monitored, how the standard of care should be implemented in all patients and how long people should be followed up to monitor for relapse.

6.6 | Concluding remarks

The recommendations for these guidelines have been derived from a systematic review[22] of all relevant publications and where evidence was not available, the recommendations were based on expert opinion and established practice. These recommendations are aimed at health care providers treating persons with diabetes mellitus and active CNO. Early recognition of active CNO of the foot and ankle and prompt implementation of evidence-based treatment can reduce morbidity and increase the likelihood of a satisfactory outcome in individuals with active CNO. Health care professionals working as a part of a multidisciplinary team are ideally positioned to treat this disease. Offloading with a total contact cast or non-removable knee-

high device is the most important intervention with the strongest evidence available for treatment of active CNO. In people with diabetes mellitus and neuropathy who present with clinical signs of acute inflammation (redness, increased skin temperature, and oedema) and normal radiographs, advanced imaging is recommended. Currently, MRI is the best advanced imaging modality because it allows the assessment of bones, joints, ligaments and tendons. Offloading with a TCC or non-removable knee-high device should be implemented as soon as possible and should not be delayed while waiting for advanced imaging.

Our systematic review[22] has demonstrated that there is a paucity of contemporary high-quality evidence on the diagnosis, management and prognosis of active CNO. Further research is warranted to address the issues surrounding this complex problem. 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 areas of CNO. Future research should address both non-surgical and surgical management to better inform the diabetes-related foot disease community on the most effective treatment for persons with diabetes and CNO. To enable the performance of studies with sufficient quality, the core details required in the planning, the conduct and reporting of studies need to be defined and subsequently implemented in CNO research in order to make relevant progress in the management of active CNO.

AUTHOR CONTRIBUTIONS

Dane K. Wukich, Katherine M. Raspovic, Nicolaas C. Schaper and Catherine Gooday wrote the manuscript. Katherine M. Raspovic acted as the secretary of the Working Group. Dane K. Wukich acted as the chair of the Working Group. Dane K. Wukich, 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 and Eric Senneville assessed the literature, drew conclusions, and critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

Production of the 2023 IWGDF Guidelines was supported by unrestricted grants from Advanced Oxygen Therapy Inc., Essity, Mölnlycke, Reapplix, and Urgo Medical. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines and have not seen any guideline or guideline-related document before publication. All individual conflicts of interest can be found at https://iwgdfguidelines.org/charcot/.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from International Working Group for the Diabetic Foot. Production of the 2023 IWGDF Guidelines was supported by unrestricted grants from Advanced Oxygen Therapy Inc., Essity, Mölnlycke, Reapplix, and Urgo Medical. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines and have not seen any guideline or guideline-related document before publication.

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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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