Received: 24 February 2020 | Revised: 17 March 2020 | Accepted: 6 April 2020

DOI: 10.1002/dmrr.3328

WILEY

RESEARCH ARTICLE

Systematic review of techniques to monitor remission of acute Charcot neuroarthropathy in people with diabetes

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Funding information
National Institute for Health Research, Grant/Award Number: ICA-CDRF-2015-01-050

Abstract

Aim: The management of acute Charcot neuroarthropathy relies on off-loading which is costly and time-consuming. Published studies have used monitoring techniques with unknown diagnostic precision to detect remission. We performed a systematic review of techniques for monitoring response to offloading in acute Charcot neuroarthropathy.

Materials and Methods: We included studies of off-loading which evaluated or described monitoring techniques in acute Charcot neuroarthropathy. PubMed, EMBASE, CINAHL and Cochrane databases were searched (January1993-July 2018). We extracted data from papers including study design, setting, population, monitoring techniques and treatment outcomes. We also extracted information on the cost, clinical applicability, sensitivity and specificity, safety and participant acceptability of the monitoring techniques.

Results: We screened 1205 titles, 140 abstracts and 45 full-texts, and included 29 studies. All studies were of low quality and at high risk of bias. In seven studies, the primary aim was to evaluate monitoring techniques: three evaluated magnetic resonance imaging, two thermography monitoring, one three-phase bone scanning and one Doppler spectrum analysis. The remaining 22 observational studies reported treatment outcomes and described the monitoring techniques used to assess the Charcot neuroarthropathy. Heterogeneity prevented the pooling of data. Very few studies included data on cost, clinical applicability, sensitivity and specificity, safety and patient acceptability of the monitoring techniques used.

Conclusion: Multiple techniques have been used to evaluate remission in acute Charcot neuroathropathy but uncertainty remains about their effectiveness. We recommend further research into the influences of different monitoring techniques on treatment outcomes.

KEYWORDS

Charcot neuroarthropathy, monitoring, off-loading, remission, systematic review

1 | INTRODUCTION

Charcot neuroarthropathy (CN) is a complication of peripheral neuropathy associated with diabetes which affects the lower limb. It may be precipitated by minor trauma or other inflammatory insult which the patient does not notice due to insensitivity to pain. When, the patient does not rest the foot, an exaggerated inflammatory response occurs.[1] The symptoms include redness, warmth and swelling in the foot and/or leg. It can cause fractures and dislocations within the foot, which may progress to deformity and ulceration.

The treatment aims to stop the inflammatory process, relieve any pain and maintain foot structure.[2] Treatment for CN is "off-loading" the application of a non-removable plaster or fibreglass cast or boot; this rests and immobilizes the foot and redistributes the weight and pressure from the foot to the leg.[3] Off-loading is continued until remission when there are no longer clinical signs of inflammation, and X-rays are stable with signs of healing.[2]

Globally, evidence suggests significant variation in treatment times. In the United Kingdom, observational studies report treatment times of 9 to 12 months before remission is achieved[4-6] whilst data from the United States[7-10] and other European centres report treatment times of only 4–6 months.[11-16] Several factors could contribute to global variation, include participant characteristics, different techniques for monitoring, different protocols for the same monitoring techniques, variations in approach to off-loading and study design variability.[5]

The current evidence base for the treatment of CN is poor. It is principally based on small retrospective cohort and observational studies of patients attending multidisciplinary foot clinics. Evidence to support the effectiveness of techniques to monitor CN is lacking, and current practice is primarily based on expert opinion.[2] Skin temperature is used because CN involves inflammation of the soft tissue and bone.[17] Skin temperature is however, a proxy measure of inflammation measured on the dorsum of the foot over the site of injury, which may not reflect the degree of inflammation within the affected deeper tissues, bones and/or joints. X-rays show damage to the foot skeleton rather than disease activity and are a measure of foot deformity. Despite these limitations, serial temperature measurements and X-rays remain the most widely used monitoring technique in CN.

Improvements in monitoring CN could reduce treatment times. Lack of evidence to support clinicians in the choice of the type of monitoring and decision thresholds for remission may account for variability in treatment times. To the best of our knowledge, there are no systematic reviews focused on monitoring techniques to identify remission in CN.

Therefore, this systematic review aims to identify the effectiveness of published techniques for monitoring remission in the management of acute CN in patients living with diabetes. The objectives are:

1. To identify the techniques used in the monitoring of CN.
2. To identify the sensitivity and specificity of different techniques used to monitor CN.
3. To identify the financial implications to healthcare providers and the NHS and the clinical feasibility of identified techniques.
4. To identify the safety considerations, and participant acceptability of identified techniques.
5. To identify whether different techniques used for monitoring influence the outcomes of CN.

2 | METHODS

This systematic review adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist.[18] The protocol was prospectively registered in PROSPERO http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018093340(CRD42018093340).[19]

2.1 | Inclusion and exclusion criteria

The inclusion criteria for study design were purposefully wide, based on prior knowledge of research studies on CN. We included randomized controlled trials, preference-controlled trials, and observational studies with or without control group(s). We excluded abstracts, systematic reviews and meta-analyses, studies on surgical and pharmacological management of CN, expert opinion, observations of single case studies and laboratory studies.

We included studies on off-loading which evaluated or reported monitoring techniques in adults with diabetes with a diagnosis of acute CN managed in any setting, including hospital, primary care or community. The control condition included other techniques used to monitor CN or the same technique used differently, for example different protocols for thermographic monitoring.

2.2 | Search strategy

We completed searches in PubMed, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. The searches were restricted to English language, from 1993 to June 2018 and adapted for each database. See Appendix 1 for an example search strategy for PubMed. We used search terms for diabetes, Charcot, neuroarthropathy and osteoarthropathy. We also checked the reference lists of relevant published systematic reviews.

We downloaded all papers identified into EndNote and removed duplicates. Screening was conducted independently by two reviewers (C.G. and K.G.) in all three phases: title, abstract and full-text screening. Reasons for exclusion were recorded during abstract and full text screening. Inter-rater agreement was calculated by the number of papers on which the two reviewers agreed in terms of inclusion and exclusion, divided by the total number of double screened papers. Discrepancies were resolved by consensus (C.G. and K.G.). All records deemed eligible following this consensus process were included for full text assessment or data extraction.

We extracted information on participant characteristics including type of diabetes, duration and HbA1c. We also extracted information

on sensitivity and specificity of the techniques, protocol for application of the technique, costs and feasibility, safety and participant considerations. Finally, we extracted methods of off-loading and clinical outcomes such as time to healing and relapse rates.

The first author (C.G.) extracted data from all included papers. The completed data extraction sheets were independently validated by a second reviewer (K.G.) against the papers. Given the wide range of study designs included, data synthesis was narrative.

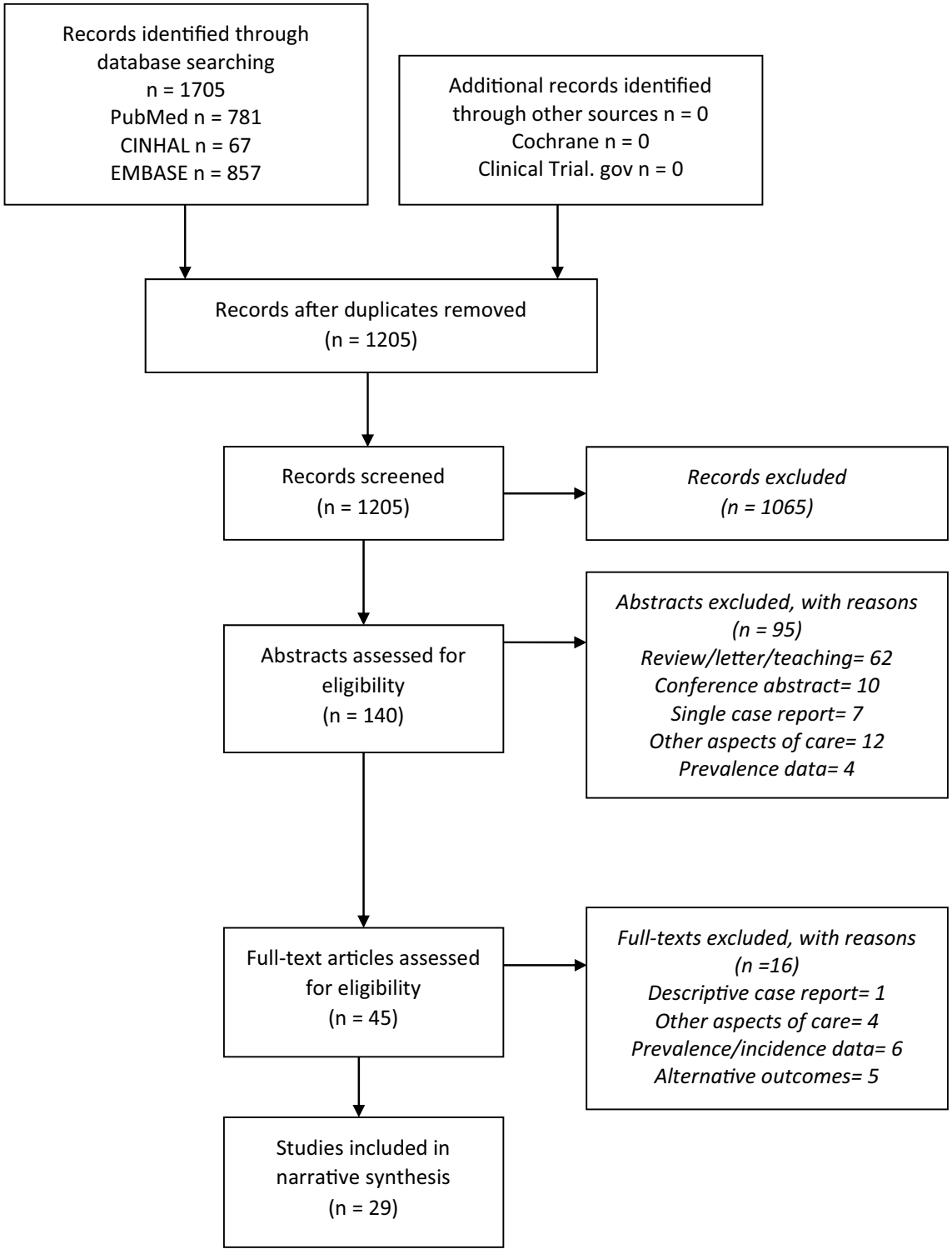

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses diagram

3 | RESULTS

3.1 | Search results

After removal of duplicates, we identified 1205 papers (Figure 1) and excluded 1065 during title screening. During abstract screening we excluded 95/140 papers, most exclusions concerned reviews, papers describing other aspects of care and conference abstracts. Inter-rater agreement during title screening was 94.1% (1134/1205), and 81.4% (114/140) during abstract screening 87% (39/45). Forty-five full text papers were screened; most common exclusion reasons were that studies described other aspects of care, and outcomes or were epidemiological reports.

TABLE 1 Included studies and evidence grades

Studies evaluating monitoring	Evidence grading
Armstrong et al.[38]	Level 3
Chantelau et al.[21]	Level 3
McGill et al.[22]	Level 3
Moura-Neto et al.[23]	Level 3
Schlossbauer et al.[24]	Level 3
Wu et al.[25]	Level 3
Zampa et al.[11]	Level 3
Studies evaluating off-loading which describe monitoring	**Evidence grading**
Armstrong et al.[10]	Level 3
Chantelau.[12]	Level 2
Chantelau and Richter.[26]	Level 3
Christensen et al.[13]	Level 3
de Souza.[8]	Level 3
Dixon et al.[27]	Level 3
Fabrin et al.[14]	Level 3
Holmes and Hill.[28]	Level 3
O'Loughlin et al.[29]	Level 3
Osterhoff et al.[30]	Level 2
Pakarinen et al.[31]	Level 3
Parisi et al.[32]	Level 3
Renner et al.[15]	Level 2
Ruotolo et al.[16]	Level 3
Pinzur et al.[9]	Level 3
Saltzman et al.[33]	Level 3
Sinacore.[7]	Level 3
Stark et al.[6]	Level 3
Thewjitcharoen et al.[34]	Level 3
Verity et al.[35]	Level 3
Visan et al.[36]	Level 3
Wukich et al.[37]	Level 2

We included 29 papers (Table 1). We used the Scottish Intercollegiate Guidelines Network criteria for assigning level of evidence. Three papers were case control and one a cohort study, that is, level 2 studies. The remaining 25 were level 3, non-analytic case series. Ten studies were prospective and the remaining 19 retrospective reviews of medical records. All included studies were of low or very low quality.

3.2 | Study and participant characteristics

Eight studies were conducted in the United States, four studies in Germany, and two in Denmark, Switzerland, Italy, and Brazil (Table 2). In total, 1132 participants were included across all studies with 1239 episodes of CN. Mean sample size was 39 (±27 range 13-115). The studies collected data for between 4 months and 23 years.

The mean age of participants was reported in 20 studies and ranged from 52 to 62.5 years old. Participants' sex was reported in 26 studies: 56% (614/1095) who experienced an episode of acute CN in these studies were male (range 4-68). Twenty-three studies clearly reported the type of diabetes. 67.7% (598/896) of participants with acute CN had a diagnosis of type 2 diabetes (range 5-84). The mean duration of all types of diabetes ranged from 13.0 to 24.5 years. Any data reported on severity and anatomical location of the CN are reported in Table 2.

We divided the studies into two groups. In the first group, the evaluation of monitoring techniques was the study's primary aim, so likely to report data to address the first four objectives on the efficacy and acceptability of the techniques.[11,21-25,38] In the second group, the study's primary aim was to report outcomes of CN but they may also describe monitoring techniques used, thus providing data to answer our fifth objective on whether monitoring techniques influence outcomes.[6-10,12-16,26-37]

3.3 | Techniques used in the monitoring of CN

Table 3 summarizes the protocols used to monitor CN. Of the seven studies included in the first group, three evaluated magnetic resonance imaging (MRI) for monitoring CN.[11,21,24] The first study compared dynamic MRI, with gadolinium contrast medium, every 3 months with foot skin temperature measured with a handheld infrared temperature scanner and midfoot and ankle circumference in 40 participants with CN.[11] The authors concluded that contrast medium uptake rate obtained with dynamic-MRI represents a reliable technique for predicting remission in acute CN. Intra- and inter-observer agreement for assessment of contrast medium uptake was high: correlation (k) = 0.96. The authors reported a 90% agreement between clinical findings and MRI. The mean healing time at clinical examination was 6.8 ± 2.3 months and 8.3 ± 2.9 at MRI. In 23% of participants, the clinical signs of disease stabilization were found 3 to 6 months prior to the stabilization observed on MRI. The second study retrospectively reviewed the notes and images of 45 episodes of CN over 23 years.

TABLE 2 Study and patient characteristics

Studies evaluating monitoring						
Author, year and country of study	**Study design and time frame for data collection**	**Inclusion and exclusion criteria**	**Sample size and CN classification**	**Participant characteristics**		
				Age	**Sex**	**Diabetes**
Armstrong and Lavery (1997) USA	Retrospective observational study without controls 1993-1994 (2 years)	*Inclusion* Diagnosis of DM Acute CN *Exclusion* Osteomyelitis Extending to bone Chronic CN Open reduction of fracture	39 participants *Sanders & Frykberg's* I = 2.6% II = 64.1% III = 25.6% IV = 7.7% V = 0%	Age years mean (SD) = 59 (9.5)	Male n = 20 (51%) Female n = 19 (49%)	T1DM n = 1 (2.6%) T2DM n = 38 (97.4%) DM duration mean (SD) = 16.5 (4.9)
Chantelau et al (2018) Germany	Retrospective observational study without controls 1994 to 2017 (23 years)	*Inclusion* Active stage CN based on typical clinical and MRI findings *Exclusion* Cases with skin defects or infections Non-compliant patients Insufficient clinical documentation	37 participants 45 feet *Modified Eichenholtz* 0 = 17 (38%) I = 28 (62%) II = 0 III = 0	Age years median (range) = 59 (37-81)	Male n = 21 (57%) Female n = 16 (43%)	T2DM = 19 (51%) T1DM = 17 (46%) No diabetes = 1 (3%)
McGill et al (2000) Australia	Prospective observational study with controls Time frame not reported	*Inclusion* Acute unilateral CN *Exclusion* Not reported	17 participants 8/17 participants received bone scans every 3 months maximum 12 months	Age years median (IQR) = 58.5 (53.5-65.5)	Not reported	T2DM = 13 (75%) T1DM = 4 (25%) DM Duration median (IQR) = 13.5 (7-19.5)
Moura-Neto et al (2012) Brazil	Prospective observational study without controls 2007-2009 (3 years)	*Inclusion* Acute Charcot foot *Exclusion* Not reported	28 participants Brodsky 1 = 71.40% 2 = 17.90% 3A = 0% 3B = 0% 4 = 10.7% 5 = 0%	Age years mean (SD) = 58.8 (11.7)	Male n = 14 (50%) Female n = 14 (50%)	T2DM n = 28 (100%) DM duration mean (SD) = 14.3 (5.1)
Schlossbauer (2008) Germany	Prospective observational study without controls Time frame not reported	*Inclusion* Acute clinical signs of CN *Exclusion* Foot ulcers Previous foot surgery Fractures Apparent deformity	13 participants *Modified Eichenholtz* 0 = 13 (100%) I = 0 II = 0 III = 0	Age years mean = 61.2	Male n = 20 (51%) Female n = 19 (49%)	T1DM n = 7 (54%) T2DM n = 5 (38%) Idiopathic neuropathy n = 1 (8%) DM duration mean = 20.5

(Continues)

TABLE 2 (Continued)

Studies evaluating monitoring						
Author, year and country of study	**Study design and time frame for data collection**	**Inclusion and exclusion criteria**	**Sample size and CN classification**	**Participant characteristics**		
				Age	**Sex**	**Diabetes**
Wu et al (2012) Taiwan	Prospective observational study without controls 2001-2009 (8 years)	*Inclusion* Acute Charcot foot *Exclusion* Undergone no previous evaluation or treatment	15 participants Brodsky 1 = 40% 2 = 27% 3A = 13% 3B = 7% 4 = 13% 5 = 0%	Age years mean (range) = 55.6 (28-76)	Male n = 7 (47%) Female n = 8 (53%)	T1DM n = 4 (27%) T2DM n = 11 (73%) DM duration mean (range) = 22.2 (13-34)
Zampa et al (2011) Italy	Prospective observational study without controls 2001-no end date reported	*Inclusion* Acute Charcot foot *Exclusion* Not reported	40 participants Forefoot = 12.5% Mid-foot = 80% Hind-foot = 7.5%	Age years mean (SD) =58.3 (13)	Male n = 22 (55.5%) Female n = 18 (45.5%)	T1DM n = 17 (42.5%) T2DM n = 23 (57.5%) DM duration mean (SD) = 19.1 (12.1) HbA1c mean (SD) = 8.9
Studies evaluating offloading which describe monitoring						
Armstrong et al (1997) USA	Retrospective observational study without controls 1991-1994 (3 years)	*Inclusion* Acute Charcot foot *Exclusion* Concomitant osteomyelitis Chronic CN Bilateral CN Open reduction of fracture	55 participants 60 feet *Sanders & Frykberg's* I = 3% II = 48% III = 34% IV = 13% V = 2%	Age years mean (SD) = 58.6 (8.5)	Male n = 27 (49%) Female n = 28 (51%)	T1DM n = 1 (2%) T1DM duration = 12 T2DM n = 54 (98%) T2DM duration mean (SD) = 15.9 (5.7)
Chantelau (2005) Germany	Case control study 1997-2004 (7 years)	*Inclusion* Clinical signs of CN. Selected if fractures were undetected on first plain X-ray after onset of symptoms or presumed OA changes in only one WB joint *Exclusion* Previous CN on the same foot Active ulceration Patients defaulting from clinic before complete healing	24 participants Unable to summarize from paper	Age years; early initiation treatment group mean (range) = 61 (44-73) Age years; late initiation treatment group mean (range) = 52 (28-73)	Male n = 13 (54.2%) Female n = 11 (45.8%)	T1DM n = 8 (33%) T2DM n = 16 (77%) DM duration median early initiation treatment group (range) = 25 (3-53) DM duration median late initiation treatment group (range) = 14 (3-32)
Chantelau and Richter (2013) Germany	Retrospective observational cohort study without controls	*Inclusion* Cases treated and followed up by the diabetic foot clinic until healing *Exclusion*	59 participants 71 feet Forefoot = 18 (25%) Midfoot = 48 (68%)	T1DM Age years median (range) = 55 (48.5-59.5)	Male n = 30 (50.1%)	T2DM n = 35 (59%) T2DM duration median (range) = 10 (5-19)

TABLE 2 (Continued)

	2000-2012 (12 years)	Cases with coexisting plantar ulceration or possible septic skeletal pathology	Hindfoot = 5 (7%) *Modified Eichenholtz* 0 = 27 (38%) I = 44 (62%) II = 0 III = 0	T2DM Age years median (range) = 62 (56-59)	Female n = 29 (49.9%)	T1DM n = 24 (40.1%) T1DM duration median (range) = 32 (25.5-41)
Christensen et al (2012) Denmark	Retrospective observational study without controls 2000-2005 (5 years)	*Inclusion* Persistent swelling of the foot and an increase skin temperature of more than 2°C with spontaneous onset over a few days or following minimal trauma or sudden overuse of the feet *Exclusion* Not reported	56 participants Forefoot = 15 (26.8%) Midfoot = 31 (55%) Heel = 3 (5%) Ankle = 7 (12.5%)	Age years mean (SD) = 58.3 (11.6)	Male n = 33 (59%) Female n = 23 (41%)	T2DM = 32 (57%) T2DM duration mean (SD) = 17.1 (7.8) T1DM = 24 (43%) T1DM duration mean (SD) = 34.4 (13) DM duration mean (SD) = 24.5 (13.6) HbA1c mean (SD) = 8.9 (1.7)
De Souza (2008) USA	Retrospective observational study without controls 1998-2006 (18 years)	*Inclusion* Charcot of the foot and ankle *Exclusion* Irregular attendance Noncompliance Inadequate/lost radiographs Inadequate follow up	27 participants 34 feet *Brodsky* *1 = 17* *2 = 8* *3A = 7* *3B = 0* *4 = 0* *5 = 0*	Not reported	Male n = 6 (22%) Female n = 21 (78%)	T2DM = 17 (65%) T1DM = 9 (35%)
Dixon et al (2017) New Zealand	Retrospective observational case series study without controls 2000-2014 (14 years)	*Inclusion* Not reported *Exclusion* Not reported	41 participants	Age years mean (range) = 54 (34-73)	Male n = 28 (68%) Female n = 13 (32%)	T2DM = 31 (76%) T1DM = 10 (24%) DM duration median (range) = 15 (1-47) HbA1c median (range) = 70 (36-178)
Fabrin et al (2000) Denmark	Retrospective observational case series study without controls 1984-1994 (10 years)	*Inclusion* 107 patients presenting a red, hot swollen foot with spontaneous onset who exhibited radiological evidence of osteoarthropathy. Eight patients with typical Charcot rocker bottom deformity that had developed over a period of some months in adult life with radiological evidence of Charcot *Exclusion* Deformities caused by bone fractures related to accidents were not included	115 participants 140 feet	Age years median (range) = 54 (27-80)	Male n = 59 (51%) Female n = 56 (46%)	T2DM = 21 (18%) T2DM duration median (range) = 8 (0-19) T1DM = 94 (82%) T1DM duration median (range) 22 (0-50) HbA1c median (range) = 9.4 (5.6-14)
Holmes and Hill (1994)	Retrospective observational	*Inclusion* Fracture/dislocations of the foot and ankle	18 participants		Male n = 11 (61%)	T1DM = 1 (6%) T2DM = 17 (94%)

(Continues)

TABLE 2 (Continued)

USA	case series study without controls 1985-1990 (4 years 6 m)	*Exclusion* Not reported	20 fracture/ dislocations Forefoot = 2 (10%) Mid-foot = 7 (35%) (including base second metatarsal) Hind-foot = 5 (25%) Ankle = 6 (30%)	Age years mean (range) = 55 (38-78)	Female n = 7 (39%)	
O'Loughlin et al (2016) Ireland	Retrospective observational case series study without controls 2006-2012 (6 years)	*Inclusion* Not reported *Exclusion* Not reported	40 participants	Age years mean (SD) = 58 (10)	Male n = 27 (68%) Female n = 13 (32%)	T1DM = 11 (27%) T2DM = 29 (73%) DM duration mean (SD) = 15 (9) HbA1c mean (SD) = 65 (16)
Osterhoff et al (2013) Switzerland	Retrospective case control study 2005-2012 (7 years 6 m)	*Inclusion* Diagnosed with acute CN; Echienholz's stages 0-2. Non-diabetes related CN included in the analysis *Exclusion* Echienholz's stage 3 at diagnosis Follow up <3 months after casting Immunosuppressive or osteoactive medication Post-arthrodesis of the foot before the onset of CN Amputation proximal to the Lisfranc joint during treatment	52 participants 57 feet *Sanders & Frykberg's* I = 10 (18%) II = 30 (53%) III = 13 (23%) IV = 3 (5%) V = 1 (2%)	Age years mean (SD) = 59 (11)	Male n = 36 (69%) Female n = 16 (31%)	Not reported
Pakarinen et al (2002) Finland	Retrospective observational case series study without controls 1994-2000 (6 years)	*Inclusion* Not reported *Exclusion* Not reported	32 participants 36 feet *Sanders & Frykberg's* I = 5 (%) II = 31 (%) III = 0 (%) IV = 3 (%) V = 1 (%) 11% more than 1 area involved *Modified Eichenholtz* I = 29 (80.5%) II = 2 (5.5%) III = 5 (14%)	Not reported	Male n = 22 (69%) Female n = 10 (31%)	NIDDM = 19 (59%) NIDDM duration mean (range) = 14 (1-28) IDDM = 13 (41%) IDDM duration mean (range) = 28 (8-58) HbA1c mean = 9.4%
Parisi et al (2013) Brazil	Prospective observational study without controls 2004-2009 (5 years)	*Inclusion* Patient with type 2 diabetes CN Eichenholtz stages I and II without previous treatment Abnormalities in the neuropathy evaluation Endocrinology follow-up Compliance with the proposed treatment protocol Regular follow-up with the institution's social services. *Exclusion*	22 participants	Age years mean (range) = 56 (47-64)	Male n = 7 (32%) Female n = 15 (68%)	T2DM = 22 (100%) DM duration mean (range) = 13 (8-25)

TABLE 2 (Continued)

		Presence of plantar foot ulcer at initial evaluation Preceding surgical procedure on affected foot Preceding osteomyelitis Presence of rheumatological and immunological diseases or alcoholism Patients on haemodialysis Contralateral limb amputation Pregnancy Cognitive impairment				
Pinzur et al (2006) USA	Prospective observational study without controls Time frame not reported	*Inclusion* First occurrence of CN as diagnosed by the original Eichenholtz criteria ≥40 years age Diabetes CN localized to the mid-foot Peripheral neuropathy Deformity within defined criteria No more than 1 superficial ulcer ≤3 cm Also, radiographic angle criteria *Exclusion* Pacemaker or defibrillator Full thickness foot ulcer or exposed bone History of osteomyelitis in the involved foot Inflammatory arthritis, malignancy, dialysis, oral corticosteroid therapy during the 6 months before entry Organ transplant Prior foot surgery for infection Contralateral amputation Pregnancy or lactating	10 participants (1 dropped out before completion of treatment)	Age years mean (range) = 58.2 (39-72)	Male n = 4 (44%) Female n = 5 (56%)	DM duration mean (range) = 16.4 (7-30)
Renner et al (2016) Switzerland	Retrospective case control 2002-2012 (10 years)	*Inclusion* T1DM or T2DM Peripheral neuropathy *Exclusion* Immunosuppressive or osteoactive medication Osteodestructive bone pathologies Osteomyelitis Idiopathic osteoarthropathy	90 participants 101 feet *Sanders & Frykberg's* I = 12 (12%) II = 35 (35%) III = 13 (13%) IV = 6 (6%) V = 2 (2%) I & II = 6 (6%) II & III = 1 (1%)II & IV = 24 (24%)III & IV = 3 (3%)IV & V = 2 (2%) *Modified Eichenholtz* 0 = 9 (9%) I = 61 (60%) II = 21(21%)	Age years mean (SD) = 60.7 (10.6)	Male n = 68 (76%) Female n = 22 (24%)	Not reported

(Continues)

TABLE 2 (Continued)

			III = 10 (10%)			
Ruotolo et al (2013) Italy	Prospective observational study without controls 2006-2011 (4.5 years)	*Inclusion* Acute onset of swelling, redness and warmth of the ankle and/or foot, without any bone involvement at standard X-ray. *Exclusion* Charcot joint and previous or concomitant foot ulceration Bone fractures Foot deformity Peripheral arterial disease.	25 participants *Modified Eichenholtz* 0 = 25 (100%) I = 0 II = 0 III = 0	Age years mean (SD) = 58.12 (12.94)	Male n = 16 (64%) Female n = 9 (36%)	T2DM = 19 (76%) T1DM = 6 (24%) DM duration mean (SD) = 18.87 (10.3)
Saltzman et al (2005) USA	Retrospective observational case series study without controls 1983-2003 (20 years)	*Inclusion* Primary diagnosis of CN requiring treatment of bony collapse Minimum 6-month follow-up *Exclusion* CN from other causes Patients with diabetes who had fractures that healed in the normal time without evidence of progressive fragmentation, dissolution or displacement	115 participants 127 feet *Modified Eichenholtz* 0 = 5 (4.3%) I = 59 (51.3%) II = 15 (13%) III = 11 (9.6%) IV = 6 (5.2%) No Classification = 19 (16.5%) Forefoot = 15 (%) Midfoot = 66 (%) Hindfoot = 10 (%) Ankle = 22 (%) No Classification = 4 (%) (2 pts had 2 sites)	Age years median (range) = 52 (21.1-84.6)	Male n = 43 Female n = 72 (60.5%)	T2DM = 84 (74%) T1DM = 31 (26%) DM duration median (SD) = 21 (0-36)
Sinacore (1998) USA	Prospective case control study 1991-1996 (5 years)	*Inclusion* Acute onset of swelling, redness and warmth if the ankle of foot requiring medical attention and referrals with a diagnosis of acute CN *Exclusion* Not diagnosed with DM Not referred by an orthopaedic surgeon from the author's medical facility.	30 participants 35 episodes CN Forefoot = (20%) Midfoot = (46%) Hindfoot = (23%) Ankle = (11%)	Age years mean (SD) = 55 (9)	Male n = 24 (80%) Female n = 6 (20%)	T2DM = 21 (71%) T1DM = 9 (29%) DM duration mean (SD) = 21 (12)
Stark et al (2016) UK	Retrospective observational study without controls 2007-2012 (5 years)	*Inclusion* Acute CN must have developed within the study period, and the patients must have been managed as an acute CN. *Exclusion* Patients were excluded if an acute CN was deemed unlikely from the history and clinical examination, or if imaging studies were negative or another diagnosis was found to be causative or more likely.	50 participants Forefoot = (11.9%) Mid-foot = (64.3%) Hind-foot = (19.1%) Multiple = (4.8%)	Age years mean (SD) = 62.5 (11.7)	Male n = 34 (68%) Female n = 16 (32%)	T2DM = 39 (78%) T2 DM duration median (IQR) = 15 (4.5, 20) T2DM HbA1c mean (SD) = 64 (20) T1DM = 11 (22%) T1DM duration median (IQR) = 32 (19.8, 38)

TABLE 2 (Continued)

						T1DM HbA1c mean (SD) = 70 (19)
Thewjitcharoen et al (2018) Thailand	Retrospective observational case series study without controls 2000-2016 (16 years)	*Inclusion* Presence of a hot swollen foot with or without erythema of the overlying skin after the exclusion of conditions resembling Charcot foot *Exclusion* Not reported	40 participants – 13 with acute CN *Sanders & Frykberg's* I = 12.5% II = 50% III = 27.5% IV = 5% V = 2.5%	Age years mean (SD) = 56.1 (9.2)	Male n = 4 (30.8%) Female n = 9 (69.2%)	T2DM = 12 (92.3%) T1DM = 1 (7.7%) DM duration mean (SD) = 16.6 (8.3) HbA1c mean (SD) = 9.1 (2.3)
Verity et al (2008) Canada	Prospective observational study without controls 33 month period	*Inclusion* Not reported *Exclusion* Abscess or infection Gross instability that was managed with surgical debridement or stabilization	21 participants 25 feet *Brodsky* *1 = 13 (52%)* *2 = 2 (8%)* *3A = 1 (4%)* *3B = 1 (4%)* *4 = 7 (28%)* *5 = 1 (4%)* *Modified Eichenholtz* 0 = 0 I = 8 (32%) II = 11 (44%) III = 6 (24%)	Age years mean (SD) = 52 (12)	Male n = 10 (48%) Female n = 11 (52%)	T2DM = 12 (57%) T1DM = 8 (38%) No diabetes = 1 (5%) DM duration mean (SD) = 21 (10)
Visan et al (2012) Romaninia	Prospective observational study without controls 2007-2011 (3 years 8 m)	*Inclusion* Not reported *Exclusion* Not reported	34 participants 42 feet *Modified Eichenholtz* 0 = 0 I = 29 (69%) II = 11 (26%) III = 2 (5%)	Age years mean (SD) = Not reported	Male n = 28 (67%) Female n = 14 (33%)	Not reported
Wukich et al (2011) USA	Retrospective cohort study without controls 2005-2009 (5 years)	*Inclusion* To be included in this study, radiographs taken at the onset of symptoms must not have demonstrated any fractures of the foot or ankle *Exclusion*	20 participants 22 feet 15 progressed to CN *Modified Eichenholtz* 0 = 22 (100%) I = 0 II = 0 III = 0 Forefoot = 0 Midfoot = 12 Hindfoot = 5 Ankle = 5 Multiple = 5	Participants who did progress to CN. Age years mean = 53.5	Not reported	Not reported

Abbreviations: CN, Charcot neuroarthropathy; DM, diabetes mellitus; IDDM, insulin dependent diabetes mellitus; IQR, interquartile range; MRI, magnetic resonance imaging; NIDM, non-insulin dependent diabetes mellitus; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

TABLE 3 Protocols for monitoring CN

Author (year)	Protocol for temperature measurement	Protocol for X-ray	Protocol for MRI	Protocol for other monitoring techniques described
Studies evaluating monitoring				
Armstrong and Lavery (1997)	Device: Exergen Acclimatization: 15 minutes Number Sites: 7 Repetitions: NR Frequency: NR Ambient air temperature controlled	No report of it been used	No report of it been used	No report of it been used
Chantelau et al (2018)	Not measured objectively, but rated semi quantitatively by bi-manual comparative palpation, and by inspection	Used; no details reported	Standard institution's routines, conventional MRI studies of the foot were commissioned irrespective of an expertise with the diabetic Charcot foot.	Swelling, deformity, joint dysfunction, skin abnormality were not measured objectively, but rated semi-quantitatively by palpation and inspection
McGill et al (2000)	Device: Dermatemp, Exergen Corporation, Mass, USA Skin temperature of the affected foot was measured at the hottest point. 3 months during the study.	Used at diagnosis	No report of it been used	Quantitative bone scanning. We injected 40 MBq of 99mTcEHDP intravenously, delivering only 11 MRems per scan. A standard of 10 ± 20 MBq was used to decay correct all counts. All images were taken using a low energy all purpose collimator. Isotope uptake in a standardized rectangular area over the affected foot was quantified for each of the three phases.
Moura-Neto et al (2012)	Device: Minitemp, Raytec Reference Armstrong 1997 for protocol	Frequency: monthly	No report of it been used	No report of it been used
Schlossbauer (2008)	Used no details reported	No report of it been used	1T Magnetom Harmony scanner (Siemens Medical Solutions, Erlangen, Germany). A dedicated foot and ankle coil was used. T1 fat-suppressed imaging was performed after injection of contrast.	Presence or absence of pain, erythema, oedema
Wu et al (2012)	No report of it been used	Frequency: 4 weekly	No report of it been used	Doppler spectra of the first dorsal metatarsal arteries in both feet were obtained using a 10 MHz linear ultrasound probe (ATL HDI3000 or HDI5000: ATL, Bothel, Washington). 2 weekly intervals Swelling, warmth and erythema were recorded

TABLE 3 (Continued)

Author (year)	Protocol for temperature measurement	Protocol for X-ray	Protocol for MRI	Protocol for other monitoring techniques described
Studies evaluating monitoring				
Zampa et al (2011)	Device: not stated Technique: hottest point by a hand-held infrared temperature scanner	No report of it been used	Tesla: 1.5 Frequency: 3 monthly Contrast: yes Time: 16 ± 4 minutes	Ankle and midfoot circumference
Studies evaluating off-loading which describe monitoring				
Armstrong et al (1997)	Device: Exergen Reference Armstrong 1997 for protocol	Used; no details reported	No report of it been used	No report of it been used
Chantelau (2005)	No report of it been used	Used; no details reported	Used; no details reported	Bone technetium scan and CT used in diagnosis
Chantelau & Richter (2013)	Foot temperature – palpated to the contralateral foot	Used: performed as appropriate	T1 weighted, T2 weighted and STIR imaging had been carried out, with or without contrast media, at the discretion of the radiologist in charge. MRI was repeated in each patient for monitoring of the healing process at the discretion of the diabetic foot clinic.	Foot oedema – by inspection and palpation in comparison to the contralateral foot, (photography used) Foot deformity – inspection and palpation in comparison to the contralateral foot (photography used). Depression of longitudinal arch was graded
Christensen et al (2012)	Device: not reported Highest area identified and compared with the identical area on the contralateral foot. Frequency: 2-6 weeks	No report of it been used	No report of it been used	Bone scintigram following i.v. injection of pertechnetate used in diagnosis
De Souza (2008)	Infrared thermometers, and skin thermistors were not used. Meticulous palpation with the palm and the back of the hand and fingers was used to assess decreased warmth.	Frequency: 2 week intervals early phases of treatment, then less frequently.	No report of it been used	No report of it been used
Dixon et al (2017)	No report of it been used	Used; no details reported	Used; no details reported	No report of it been used
Fabrin et al (2000)	Device: Thermocouples medical precision thermometer DM 852: Thermocouples, Ellab, Copenhagen). Frequency: 2-6 weeks	Frequency: 6-12 weeks	No report of it been used	No report of it been used
Holmes and Hill (1994)	No report of it been used	Used; no details reported	No report of it been used	No report of it been used
O'Loughlin et al (2016)	No report of it been used	No report of it been used	No report of it been used	No report of it been used

(Continues)

TABLE 3 (Continued)

Studies evaluating off-loading which describe monitoring				
Osterhoff et al (2013)	No report of it been used	Used; no details reported	MRI used to confirm diagnosis and if uncertainty remained regarding inflammation	Osseous biopsies used to confirm diagnosis
Pakarinen et al (2002)	Skin temperature and temperature differences between the affected and non-affected foot were measured	Used; no details reported	Diagnostic and follow-up MRIs were performed	No report of it been used
Parisi et al (2013)	Device: not reported Local temperature Every 15 days during the first 12 weeks then monthly	Standardized radiographic evaluations. Every 15 days during the first 12 weeks then monthly	No report of it been used	No report of it been used
Pinzur et al (2006)	No report of it been used	Used; no details reported	No report of it been used	Objective measure of water displacement at each visit Clinical assessment of soft-tissue swelling (non, mild, moderate, severe) Midfoot stability (stable, moderately unstable, unstable)
Renner et al (2016)	Redness and warmth measured by visual inspection and palpation	No report of it been used	Confirmation of CN by magnetic resonance imaging (MRI; ie, soft tissue oedema, joint effusion and/or subchondral bone marrow oedema of involved joints characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images)	No report of it been used
Ruotolo et al (2013)	Device: portable infrared thermometric probe Frequency: 3 weekly Reference Armstrong 1997 for protocol	Used at diagnosis no details reported	Used to confirm healing 1.5T Pre-contrast T1WTSE Ax, T2WTSE Ax, T2WFFE SAG, T2 STIR COR, T1 SPIR AX: Post-contrast T1WTSE AX, T1 SPIR AX, T1 SPIR SAG optional.	F-FDG PET/CT scan Scans were examined visually for focal abnormalities, and data generated from the scan were also assessed quantitatively by calculating the maximum standard uptake value Frequency: 3 monthly
Saltzman et al (2005)	No report of it been used	Used; no details reported	No report of it been used	No report of it been used
Sinacore (1998)	Reduction in swelling, a decrease in local skin/tissue temperature and reduced skin erythema.	Used; no details reported	No report of it been used	No report of it been used
Stark et al (2016)	Device: not reported Frequency: 1-2 weeks	Used; no details reported	Used; no details reported	No report of it been used
Thewjitcharoen et al (2018)	No report of it been used	No report of it been used	No report of it been used	No report of it been used

TABLE 3 (Continued)

Studies evaluating off-loading which describe monitoring					
Verity et al (2008)	Resolution of swelling, erythema and increased warmth) No details reported Frequency: monthly	Frequency: monthly	No report of it been used	No report of it been used	
Visan et al (2012)	No report of it been used	Used; no details reported	No report of it been used	No report of it been used	
Wukich et al (2011)	No report of it been used	No report of it been used	No report of it been used	No report of it been used	

They reviewed sequential follow-up MRIs to assess the change in oedema equivalent signal change during treatment for CN with a walking cast. The number of follow-up MRIs per episode of CN ranged from 1 to 6. They found decreasing oedema-equivalent signal change in 69% (66/95) of follow-up MRIs but reported a combination of physiologic and pathologic fluctuations in oedema equivalent signal change in the remainder of the MRIs.[21] The third study compared bone marrow oedema on MRI at baseline and after 4 months, and correlated this to symptoms of CN in 13 participants. There was a statistically significant decrease in bone oedema over 4 months, with a statistically significant correlation between pain and soft tissue oedema and the bone marrow oedema over the same timescale.[24]

Two studies evaluated infrared thermometry to identify disease remission.[23,38] The first study described in detail the protocol for measuring temperature using the Exergen Model DT 1001. They controlled for ambient room temperature, allowed a 15 minute acclimatization period, and measured seven sites on the foot, compared with the contralateral limb as the physiologic control, at monthly intervals.[38] Casting was discontinued based on reduction or absence of clinical signs of inflammation, radiologic signs of healing and when the temperature difference between feet had stabilized with a cut-off point of less than 4°F (2.2°C) difference. The authors report that the choice of the cut-off figure was based on clinical experience The second study referenced the protocol described by Armstrong and Lavery[38] for measuring temperature but used the Minitemp, Raytec[23] to monitor temperature. Casting was discontinued when the temperature difference between feet was recorded as less than 2°C.

One study evaluated Doppler spectrum analysis as a novel diagnostic tool for planning treatment.[25] The study compared the Doppler spectra of the first metatarsal arteries in both feet using a 10 MHz linear ultrasound probe (ATL HDI3000 or HDI5000; ATL, Bothel, Washington). The Doppler spectra in the unaffected limb were triphasic, compared to the affected limb which showed monophasic forward flow. The Doppler spectra analysis was repeated every 2 weeks in the affected limb until it returned to normal. At this point, participants either started weight-bearing or underwent surgical reconstruction of the ankle joint. The authors concluded that Doppler spectra analysis of the foot may be used as a guide to begin weight bearing. They reported a discrepancy between the two monitoring techniques: only four out of 15 patients had X-rays which showed healing when the foot was healed according to the Doppler Spectra analysis.

In the final study, a subset of eight participants from a larger study received three monthly three-phase quantitative bone scans of both feet for a maximum of 12 months. They compared the ratio of isotope uptake between feet, between the affected foot and the tibia and compared isotope uptakes to the clinical indicators of inflammation. There was strong correlation between temperature difference and the ratio of isotope uptake in the affected vs unaffected foot, the perfusion of the affected foot in the dynamic phase and the isotope uptake in the delayed phase of the bone scans.[22] The study also reported on the change in temperature difference between the affected and unaffected foot from baseline 3.3°C, at 6 months 1.3°C, and at 12 months 0.8°C noting a progressive decrease over time.[22]

TABLE 4 Treatment and outcomes of CN

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Armstrong and Lavery (1997)	Infrared dermal thermometry TCC	Mean (SD) = 26.6 m (7.1)	Mean skin temperature difference for all subjects at initial presentation 8.8 ± 2.3°F (range 5.1-14.7) At initial presentation the site of maximum skin temperature gradient correlated to the site of maximum Charcot arthropathy (radiographically) in 92% cases. The site of maximum skin temperature gradient correlated to the site of maximum Charcot arthropathy (radiographically) in 72% of all cases throughout the follow up period. Time to remission – not reported	Relapse – not reported	7.7% new onset ulceration
Chantelau et al (2018)	MRI Immobilization and offloading – cast treatment	19 cases had only 1 follow up scan 11 cases had 2 follow up scans 9 cases had 3 follow up scans 6 cases had 4–6 follow up scans Individual follow up scans were on average 13 weeks apart (range 35-50 weeks)	Not all patients were followed up until healing 140 reports (45 baseline and 95 MRI follow-up) 69% (66/95) follow up scans showed dependent regression of oedema-equivalent signal change as expected. 31% (29/95) showed stagnant or extending oedema-equivalent signal change. Proportions of follow up scans showing oedema-equivalent signal change regression was independent of the active-stage Charcot foot, severity grade, renal failure and order of the follow up scans (1st vs 2nd to 6th FUS); all chi2 $P > 0.05$. Estimated duration until 'healing' Grade 0 = 25 weeks (approx) Grade 1 = 35 weeks (approx)	5 cases	Not reported
McGill et al	Temperature measurement Quantitative bone scanning 12 months – rest and contact casting	subset 8 subjects received bone scans	At presentation, the affected foot was 3.3°C (2.4 ± 4.7) hotter than the unaffected foot. After 6 months there was 1.3°C (0.5 ± 1.9) difference.	Not reported	Not reported

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
			After 12 months, there was 0.8°C (0.3 ± 1.6) difference. Correlation (r = .90, P < .0001) between temperature difference and the ratio of isotope uptake in the affected: unaffected feet Relationship between the perfusion of the affected foot in the dynamic phase and the isotope uptake in the delayed phase of the bone scans (r = .92, P < .0001).		
Moura-Neto et al (2012)	Skin temperature CROW – instructed to weight-bear normally but to restrain from heavy physical work.	1 year	Univariant and multivariant Cox proportional hazard regression analyses for age, sex, diabetes duration and initial temperature difference showed no influence of any of these factors on the rate or time to consolidation One-year consolidation rate = 25 (89.3%) mean = 6.6 months (±2.1) Range = 3-12 months	No relapses among the 25 patients who progressed to the chronic phase	Not reported
Schlossbauer (2008)	MRI and clinical findings Mean interval for follow up MRI = 4.2 months Pressure-relieving methods like strict non-weight bearing in a brace or cast.	4 month follow-up	Bone marrow oedema in affected bones significantly decreased (P < .001) Signal intensity of bone marrow oedema in STIR imaging showed a significant correlation with the presence of soft tissue oedema and with the presence of pain at clinical evaluation (P < .05) Erythema and elevated temperature did not show a significant correlation. The presence of bone marrow oedema in the STIR sequence was strongly associated with a corresponding contrast enhancement (P < .0001)	Not reported	Not reported
Wu et al (2012)	Doppler spectrum analysis. Padded bi-valve cast and non-weight bearing	Not reported	Doppler spectrum returned normal mean = 13.6 weeks range = 6-20	1 patient relapsed after 7 weeks	3 pts underwent pan-talar arthrodesis

(Continues)

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Zampa et al (2011)	Dynamic MRI TCC	Healing or a max 12 months	Mean healing time Clinical examination = 6.8 months (±2.3) MRI = 8.3 months (±2.9) *P* = <.0001	Not reported	Not reported
Studies evaluating off-loading which describe monitoring					
Armstrong et al (1997)	TCC	1 year	mean = 18.5 weeks (±10.6) range = 4-46 weeks	15% relapsed	9 (25%) underwent corrective surgery for foot deformity
Chantelau (2005)	TCC wherever possible	Until transferred into shoes	*Early referral* median = 3 months range = 2-9 months *Late referral* median = 5 months range = 3.5-14 months *P* = > .05	Not reported	*Early referral* 1 patient developed gross foot deformity *Late referral* 13 patients developed gross foot deformity 1 skin ulcer 1 malalignment of cast foot healed in supination
Chantelau and Richter (2013)	Removable device	All patients had been followed up until transition to shoes and for variable periods of time thereafter	Stage 0 median (range) = 4 Months (2-8 months) Stage 1 median (range) = 5 months (3.5-14 months)	Not reported	9 skin ulcers 1 malalignment the foot healed in supination
Christensen et al (2012)	Removable device	Mean = 3.2 years	Mean (SD) = 141 days (±11)	3 pts (5%) had exacerbation 7 pts (12%) had recurrence at 69 days (±16)	No surgical correction of foot deformity needed
De Souza (2008)	TCC	Mean = 5.5 years Range = 1-14 years	Mean = 14 weeks Range = 4-20 weeks	Not reported	Only 1/34 had further anatomical displacement of clinical importance once it had been immobilized in a TCC

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
					Ulcers developed in 10 feet after the transfer to orthosis
Dixon et al (2017)	TCC 56%	1 year from diagnosis	Mean time until ambulatory in modified shoes = 21.3 weeks (±11.5)	2 pts a further fracture	1-year diagnosis 17 pts (34%) foot ulcer 1 pt. osteomyelitis 1 pt. underwent amputation All-cause mortality 5%
Fabrin et al (2000)	In the case of excessive swelling, a few days of immobilization in bed or in a wheelchair (sometimes in the hospital) was necessary to reduce the oedema. The routine treatment was a weight-off regimen involving 2 crutches and foot protection involving therapeutic footwear with a rigid bottom and pedal arch supports. Fitted individually with soft insoles moulded from functional imprints when necessary. Control of oedema was managed with an elastic bandage followed by compression stockings and sometimes assisted by diuretics.	Median (range) = 48 months (6-114 months)	Maintained in most cased for 4-6 months	10 pts with new attacks in the previously affected foot (time to 'new attack' not reported)	7 (6%) developed foot ulcers during a Charcot attack 2 pts underwent major amputation 3 pts underwent corrective surgery for foot deformity 2 pts died during follow-up
Holmes and Hill (1994)	Not reported	Median (range) = 27 months (14-70 months)	8/20 pts with fractures went onto develop a CN. Range healing CN pts = 7-46 months	Not reported	1 pt. with CN underwent a major amputation
O'Loughlin et al (2016)	Off-loading was administered in 50% cases. Including rest, TCC, TCI, CROW	Not reported	Not reported	Not reported	38% of pts developed subsequent ulceration

(Continues)

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
					20% pts underwent a major amputation 10% underwent corrective surgery for foot deformity
Osterhoff et al (2013)	TCC	Not reported	Not reported	13 ft (23%) Mean interval	
	recurrence = 27 months (±31) range = 3-102 months	Not reported			
Pakarinen et al (2002)	TCC	Mean = 21 months Range = 1-81 months	Mean = 11 months Range 4-37 months	Not reported	2 pts underwent major amputation 12 pts underwent corrective surgery for foot deformity
Parisi et al (2013)	Removable device. Bear weight respecting symptomatic limitations of each case.	Not reported	18 weeks	Not reported	Not reported
Pinzur et al (2006)	TCC and then removable device	1-5 months after transition into footwear	Treated with TCC mean = 5.8 weeks range = 4–10 Then aircast Total treatment time mean = 12 weeks range = 6-16 weeks	Not reported	1 Lost to follow-up
Renner et al (2016)	Mixture of TCC and removable devices	1-208 months	Unilateral mean = 20 weeks (±21) Bilateral mean = 29 weeks (±29)	Not reported	8 pts minor amputation 2 pts underwent a major amputation 4 procedures for corrective surgery for foot deformity
Ruotolo et al (2013)	TCC then removable walker	Return to prescription footwear Mean (SD) = 21.75 ± 16.7 months	Mean = 15.12 weeks (±5.45)	No recurrence reported in the follow-up time	Not reported
Saltzman et al (2005)	TCC	Median = 3.8 years Range = 0.5-18.5 years	The median time wearing an ankle-foot orthosis was 12 months (95% CI; range, 10-13 months)	Not reported	15 (11.8%) underwent a major amputation 62 (49%) recurrent ulcers

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
			27 limbs (23%) required long-term use of an ankle-foot orthosis (defined as >18 months)		36 (28%) chronically recurrent ulcers 53 corrective surgery procedures performed for foot deformity
Sinacore (1998)	TCC with crutches and advice to partial weight bear	1 month after cessation of casting	Mean = 86 days (±45) Range = 22-224	4 (13%) within first month after the initial casting period	Not reported
Stark et al (2016)	TCC and crutches	5 years	Median time to resolution for the 26 patients initially treated with a TCC was 48 weeks (95% CI: 42.4, 64.4) Median time to resolution for the 22 pts initially treated with removable offloading device of 53 weeks (95% CI: 42.5, 64.4)	15 (35%)	4 (8%) or underwent a major amputation 2(4%) died
Thewjitcharoen et al (2018)	TCC	57.1 months after the onset of the CN	Median (range) = 5 months (2-10 months)	Not reported	5 years mortality 13%
Verity et al (2008)	Removable cast or boot. Limit standing and walking to the minimum	Not reported	Mean = 29 weeks (±19) range = 6-73 weeks No remission in 8 (32%) cases	Not reported	3 feet developed new deformity
Visan et al (2012)	Removable walker	Not reported	Stage 1 4 pts at 3 months 15 pts at 6 months 5 pts after 6 months Stage 2 2 pts at 6 months 4 pts after 6 months Stage 3 1 pt at 8 months	Not reported	3 (8.83%) patients underwent surgery
Wukich et al (2011)	TCC	Median 21.7 months mean 23.6 months (±14)	19/20 (95%) diagnosis of CN missed		16/22 (72%) developed a complication 11/22 (50%) required surgical treatment

Abbreviations: CROW, Charcot restraining orthotic walker; MRI, magnetic resonance imaging; Pt, patient; Pts, patients; TCC, total contact cast; TCI, total contact insole.

In the remaining 22 studies, the primary aim was to evaluate the outcomes of CN but they described the monitoring techniques used (Table 3). The most frequent monitoring techniques used was serial X-ray in 16/22 of studies, objective temperature measurement with a handheld infrared monitoring device in 11/22 and MRI with or without contrast media in 7/22 of studies. Protocols for the same technique were not standardized across studies. For example, in studies that used infra-red skin temperature measurement to monitor CN, some studies used a cut of <1°C and others <2°C to identify remission. Some studies relied on a combination of different monitoring techniques: 5/22 described two techniques, 4/22 described three techniques and one study used four techniques to monitor CN.

Four studies used advanced radiological methods for diagnostic and/or monitoring: F-FDG PET/CT scanning,[16] bone scintigram,[13] bone biopsies[30] and isotope bone scans.[12] Other monitoring techniques included objective and subjective measures of inflammation by palpating foot temperature, and assessing the presence of swelling.[7,8,12,15,35] Another study assessed progression of foot deformity by visual examination, palpation and comparison of serial photographs.[26] Objective, serial measures of water displacement and grading of midfoot stability were used to monitor CN in another study.[9]

3.3.1 | Sensitivity and specificity of different techniques used to monitor CN

Six out of seven studies which evaluated monitoring techniques did not report the sensitivity or specificity. Zampa et al[11] reported a high intra and inter observer agreement for the assessment of contrast uptake but did not report the sensitivity of the technique. They reported that the monitoring techniques evaluated could be used as a guide to identify remission, withdraw immobilization, and begin weight bearing. None of the 22 studies reporting the outcomes of CN reported the specificity or sensitivity of the monitor techniques used to measure when the foot was in remission. Some studies relied on subjective monitoring techniques such as palpation or visual inspection of inflammation to assess for remission in CN.

3.3.2 | Financial implications to healthcare providers and clinical feasibility of different techniques

No studies reported the cost of the monitoring used in terms of capital cost to purchase equipment.

3.3.3 | Safety considerations, and participant acceptability of different techniques

Ten out of 29 studies used MRI as a monitoring tool for identifying remission of acute CN. Of these, four reported using contrast during the MRI in all or some images at the radiologist's discretion.[11,16,24,26]

A further four studies used advanced methods of radiological imaging which require the use of contrast media.[12,13,16,22] Only one of these 14 studies which used contrast specifically reported on the incidence of adverse events from the administration of the contrast, reporting no adverse events. Another study reported using bone biopsy as a diagnostic aid to confirm CN, but this was not used in monitoring.[30] They did not report any safety considerations that may be relevant to this technique. X-rays are associated with exposure to ionizing radiation, but their potential risk was not discussed in any studies. No safety considerations were reported for objective temperature measurement with a handheld infrared monitoring device or any other clinical methods for monitoring CN. None of the studies reported on participant acceptability of the monitoring techniques used.

3.3.4 | The influence of monitoring techniques on the outcomes of CN

Treatments and the definitions used to confirm remission and relapse varied between the studies. Time to healing ranged from 8 weeks to over 1 year (Table 4). Relapse rates ranged from 0% to 35% across the studies. The monitoring techniques were poorly reported and inconsistently applied across studies. Four studies did not report which techniques were used to monitor CN.

4 | DISCUSSION

The previous systematic review on assessment, diagnosis and management in CN only included papers between 2002 and 2012,[2] our review searched from 1993 to 2018 and include an additional seven studies[7,10,14,22,28,31,38] some of which are key reference papers for future studies.

To our knowledge, this systematic review is the first to synthesize the evidence base for monitoring techniques of CN and influences of different techniques for monitoring CN on treatment outcomes. We identified a heterogeneous set of 29 papers: seven specifically evaluated monitoring techniques and a further 22 described the outcomes of CN. It is not possible to conclude whether the monitoring techniques used influences the outcomes of CN. We found no high-quality studies validating the use of monitoring techniques in CN.

The key finding is the lack of a consistent approach to monitoring in CN. Common techniques included X-ray, temperature monitoring and MRI. Techniques were poorly described, and where the information was reported there was variability in the devices used and how the technique was applied. It is not clear whether the devices used were validated for the temperature ranges commonly found in feet. Some studies still rely on subjective measures of temperature difference between feet to monitor CN.[7,8,15,21,26,35]

The first paper included in this review which used temperature measurement for monitoring in CN was published in 1997.[38] The authors report that the cut-off point of 4°F (2.2°C) for healing was

not evidence-based but it appears to have been adopted as the standard for clinical decision making in subsequent studies and guidelines.[2,39] This protocol has not been validated and other studies have not specified sites, repeated measures, or acclimatization times making evaluation of studies using this technique difficult.

We found a lack of evidence on the sensitivity, specificity, cost-effectiveness, safety and patient acceptability for all monitoring techniques. There is continued uncertainty about the relationship between monitoring techniques and treatment outcomes.

In the absence of reliable evidence, we are unable to recommend any changes to current national[39] and international guidance[2] which are predominantly based on level IV evidence, that is, expert opinion.

The strengths of our systematic review include the broad range of inclusion and exclusion criteria for study type, which allowed us to describe the variability in the current approach to monitoring CN in research as well as clinical practice. Screening and data extraction were completed by two researchers who are experienced podiatrists. Our review also had some limitations: we did not search the grey literature. We limited searches to English language, we acknowledge that this may mean we missed some relevant studies and potentially introduced bias into the review. However, we feel that the impact of this would be relatively small.

In the 1990s, it was acknowledged that using subtle changes in skin temperature to inform clinical decisions may not be an accurate way to monitor CN[20] but this is still widely used in clinical practice. Further high quality research is needed to identify the optimal method of monitoring CN. We recommend that researchers accurately describe the population at baseline, standardize definitions for diagnosis and outcome measures, and provide detailed protocols for monitoring techniques in future research.

MRI as a monitoring tool for CN is increasingly acknowledged as a potentially more accurate method for monitoring and this is supported by the studies we included.[11,21,24] This warrants further investigation. An ongoing randomized feasibility study aims to explore the feasibility of using serial MRI without contrast in the monitoring of CN to decide whether a large-scale trial is warranted https://doi.org/10.1186/ISRCTN74101606.[40]

5 | CONCLUSION

Multiple techniques have been used to evaluate remission in acute CN, but the quality of published studies to support any one technique is low or very low. Uncertainty therefore remains about the effectiveness of the different monitoring techniques, and whether the different monitoring techniques influence time to remission and recurrence rates. Therefore, we are unable to make recommendations for clinical practice. There is an urgent need for high-quality studies to identify the most accurate, safe and cost-effective monitoring techniques in CN.

ACKNOWLEDGEMENTS

Catherine Gooday is funded by a National Institute for Health Research (NIHR),) ICA-CDRF-2015-01-050 Doctoral Fellowship for this research project. This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

C.G. is the NIHR Clinical Doctoral Fellow. C.G., K.G., F.G., J.W., F.P. and W.H. made substantial contributions to the conception and design of the review. C.G. and K.G. screened the papers. C.G. extracted data from all the included papers. K.G. validated data extraction. C.G. drafted the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content. All authors read, amended and approved the final manuscript.

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How to cite this article: Gooday C, Gray K, Game F, Woodburn J, Poland F, Hardeman W. Systematic review of techniques to monitor remission of acute Charcot neuroarthropathy in people with diabetes. *Diabetes Metab Res Rev*. 2020;e3328. https://doi.org/10.1002/dmrr.3328

APPENDIX A: SEARCH STRING PUBMED

Query	Items found
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms]) Filters: Publication date from 1993/01/01 to 2018/07/24; Humans; English	784
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms]) Filters: Humans; English	952
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms]) Filters: Humans	1204
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms])	1345
Search ((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy	11 189
Search osteoarthropathy	3292
Search neuroarthropathy	465
Search (charcot joint[MeSH Terms]) OR charcot	8067
Search (diabetes) OR diabetes[MeSH Terms]	633 535
Search charcot joint[MeSH Terms]	1604
Search charcot	7192
Search diabetes[MeSH Terms]	392 176
Search diabetes	633 535