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ORIGINAL ARTICLE

Prospective study of clinical, biochemical, and radiological characteristics of diabetic Charcot neuroarthropathy at a tertiary care centre

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Abstract

Objective The aim of this study was to assess demographic, clinical, biochemical, radiological profile and treatment response in diabetic patients with Charcot neuroarthropathy (CN).

Methods This was a prospective study for screening of CN in patients with diabetes mellitus (DM) attending tertiary care centre over a period of 1 year. Acute CN (ACN) was diagnosed based on clinical features of local inflammation and temperature difference of > 2 °C from the normal foot after exclusion of other inflammatory causes. Chronic CN (CCN) was diagnosed when no inflammatory signs were present in a deformed foot with radiological findings supportive of diagnosis. In all these patients, demographic data, clinical features, biochemical investigations, X-ray, and MRI foot were done. The effect of offloading and customized foot wear in ACN, CCN were, respectively, studied over 1 year.

Results Out of 5049 DM patients screened for CN over 1 year, 25 patients (0.49%) were diagnosed to have CN, of which 12 had ACN (0.23%) and 13 had CCN (0.26%). CN patients had significantly higher mean body mass index (BMI) (27.9 vs. 26.2 kg/m^2; $p = 0.02$), longer duration of DM (12 vs. 9.6 years; $p < 0.001$), higher HbA1c (10.3 vs. 8.8%; $p = 0.001$), greater degree of peripheral neuropathy and retinopathy compared to controls. MRI could be able to detect 25% ACN cases where X-rays were non-diagnostic. The median duration of clinical resolution was 3 months in ACN patients.

Conclusions High index of suspicion is required for diagnosing CN in DM patients.

Keywords Diabetes mellitus · Acute Charcot neuroarthropathy · Chronic Charcot neuroarthropathy · Clinical resolution

Introduction

Diabetic Charcot neuroarthropathy (CN) is a not a rare but a serious complication of diabetes mellitus (DM) and is often missed in early stages leading to fractures, dislocations, and deformities. Various studies have suggested that CN in addition to foot outcomes also contributes to early and higher mortality independent of foot ulcer and other comorbidities [1, 2]. Early diagnosis and appropriate offloading in acute Charcot neuroarthropathy (ACN) and customized footwear for chronic Charcot neuroarthropathy (CCN) are cornerstones in the management of CN. Neurovascular and neurotraumatic theories have been proposed as the pathogenetic mechanisms for the development of diabetic CN [3, 4]. Increased vascularity due to autonomic neuropathy, repeated unnoticed trauma because of loss of protective sensation (LOPS), increased levels of cytokines (TNF-α, IL-6), and decreased secretion of calcitonin gene-related peptide (CGRP) contributes to progressive joint and bone destruction. TNF-α and IL-6 enhance osteoclast-mediated bone resorption, which is further facilitated by decreased CGRP, increasing the ratio of receptor activator of nuclear factor kappa-B ligand (RANKL) to osteoprotegerin (OPG) in favour of RANKL, thereby inducing osteoclastogenesis [5]. The prevalence of CN in diabetic population has recently been reported to be between 0.1 and 7.5% [6]. There are very few studies which comprehensively looked into clinical, biochemical, and radiological aspects in a prospective manner and the effect of offloading in CN patients in the Indian context [7].

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The present study plans to evaluate the demographic, clinical, and biochemical characteristics unique to CN patients compared to controls and prospectively evaluate the response to total contact cast (TCC) and customized footwear in ACN and CCN patients respectively over 1 year.

Materials and methods

This study was carried out in the Department of Endocrinology, MKCG MCH, over a period of 1 year from January 2021 to January 2022. All the patients with DM visiting the Department of Endocrinology were screened for CN. ACN was diagnosed to be present when there were features of inflammation like redness, pain, tenderness, warmth along with temperature difference of > 2 °C from the unaffected foot after the exclusion of other inflammatory conditions like gout, cellulitis, osteomyelitis, rheumatoid arthritis. CCN was diagnosed to be present when foot deformity was present in the absence of inflammatory signs after exclusion of other causes of foot deformity like trauma, previous fractures, congenital deformities, with radiological features suggestive of CCN. In all these patients, a detailed demographic data and medical histories were taken including age, sex, weight, height, duration of diabetes, antidiabetic medications, hypertension, personal history of occupation, smoking habit, alcohol consumption, and employment status.

Clinical assessment included features of inflammation in the foot and temperature of the foot by infrared thermometer (Otica Meditronix Co., with accuracy ± 0.2 °C and measurement range from 0 to 100 °C). The temperature difference from the unaffected foot was assessed, and a difference of > 2 °C was defined to be significant. Detailed neurological assessment of the feet was done to detect the loss of pain, touch, vibration sensation (128 Hz tuning fork) and loss of protective sensation with 10-g monofilament. Further clinical assessment was conducted to detect the presence of callus, anhidrosis, fissures, tinea pedis, active ulceration, cellulitis, oedema, and presence of amputation at enrolment. Vascular assessment of feet was done by examining all peripheral pulses and ankle brachial index (ABI). Peripheral arterial disease (PAD) was diagnosed if ABI was less than 0.9.

Biochemical investigations including HbA1c that was estimated by high-performance liquid chromatography (HPLC) method on Bio-Rad 10 analyser, fasting plasma glucose (FPG), 2-h post-prandial plasma glucose (2-h PPG) were estimated in Seimens AUTOPAK 300 auto analyser, and lipid profile, Sr. creatinine, and Sr. urea were estimated by TOSHIBA 120 FR automated analyser. Complete blood count with ESR was done in all cases. C-reactive protein (CRP) levels and urinary spot albumin creatinine ratio (ACR) were estimated by nephelometry in a protein analyser (MISPA-i_3). Diabetic nephropathy was defined by the presence of spot urinary ACR of ≥ 30 mg/g of creatinine on two different occasions.

Radiological investigations included X-ray of both feet anteroposterior (AP) and oblique views. The modified Eichenholtz classification [8], which relies on clinical and x-ray findings, was used for staging of Charcot foot. Stages 0 (prodromal phase) and 1 (development phase) are taken as ACN, and stages 2 (coalescence phase) and 3 (consolidation phase) are taken as CCN [9].

The anatomical location of CN distribution on the affected foot was done according to Sander's and Frykberg's classification system [10]. To determine the severity of deformity in Charcot feet, Meary's angle, calcaneal pitch, and cuboid height were calculated from X-ray of foot in oblique view [3]. Meary's angle is generally close to zero degree, and Calcaneal pitch normally lies between 20 and 30° [11].

MRI foot was done in all cases of suspected CN by a single radiologist for detection of earliest lesions. MRI protocol for Charcot foot included sagittal T1, transverse T1 foot images including short tau inversion recovery (STIR), and coronal T2 hindfoot. The presence of bone marrow oedema, soft tissue oedema, bone dislocations, fragmentation, and fractures was noted in all ACN cases.

Patients with ACN were offloaded with TCC and were followed every fortnightly till clinical resolution. Clinical remission of active CN was defined as absence of inflammatory signs and temperature difference < 2 °C between the affected foot and a similar site on the opposite foot on two successive follow-up visits 2 weeks apart [12].

During each follow-up visit of ACN patients on TCC, an average of three temperature recordings at the region of interest of foot was obtained after the removal of cast for 30 min. Inflammatory markers like ESR were done at clinical resolution. MRI of feet was repeated in cases of doubtful resolution. Blood investigations like FPG, 2-h PPPG, HbA1c were done to check for the glycemic status of patients and were treated accordingly. After clinical remission of active CN, the TCC was discontinued, and participants were provided with customized footwear for Charcot foot during subsequent follow-up. Patients were reviewed for 3 months with thorough foot examination for recurrence of CN.

Customized footwear was prescribed in all CCN patients. Patients with foot ulcer were followed at 2-week interval to look for healing of ulcer or development of any complications like new ulcer formation or osteomyelitis by clinical examination and necessary investigations like X-ray foot where required. Glycemic status and progression of foot deformities were checked every 3 months in all CCN patients.

Age- and gender-matched patients with DM and without CN who consented for the study were selected as controls in

the ratio of 5:1. The study was approved by the Institutional Ethics Committee of MKCG Medical College, Berhampur. Appropriate informed consent was obtained from all study participants, and confidentiality of data was maintained throughout the study.

Statistical analysis

Statistical analysis was carried out by using Microsoft Excel 2007 (Microsoft Corp, Redmond, WA). Descriptive statistics for the categorical variables were performed by computing the frequencies (percentages) in each category. For the quantitative variables, approximate normality of distribution was assessed by using Shapiro–Wilk test. Variables following normal distribution were summarized by mean and standard deviation (SD), and the remaining variables were summarized as median (inter-quartile range [IQR]). Continuous variables were compared using Student's *t*-test and Mann–Whitney U-test, and categorical variables were compared by using χ^2-test. A *p*-value of less than 0.05 was considered statistically significant.

Results

In the present study among 5049 diabetes patients screened for CN, 25 patients were detected to have CN. Out of 25 patients with CN, one had type 1 DM and the rest 24 patients had type 2 DM. Among the 25 CN patients, 12 patients had ACN (0.23%) and 13 patients had CCN (0.26%). The control group constituted 125 age- and sex-matched DM patients without CN (Fig. 1).

The comparison of baseline characteristics of cases and controls is shown in Table 1. The mean ages of cases and controls were 55.6 ± 8.8 years and 54.7 ± 8.5 years, respectively, and were not statistically different. The CN patients had significantly higher BMI (27.9 ± 3.2 vs. 26.2 ± 2.7 kg/m2), longer duration of DM (12 ± 3.9 vs. 9.6 ± 3.5 years) and higher HbA1c levels (10.3 ± 2.4% vs. 8.8 ± 1.9%) compared to the controls. Sensory neuropathy (100% vs. 73%) and retinopathy (68% vs. 46%) were significantly more common in CN patients than controls. There was no significant difference in the prevalence of hypertension, diabetic nephropathy (urine ACR), CAD, CVA, and PAD (Table 1).

Comparing clinical features between acute and chronic CN

The mean ages of ACN and CCN patients were 52.6 ± 7.6 years and 54.4 ± 4.8 years, respectively. Median delta temperature at presentation in ACN patients was 3 °C (IQR 2.7–3.1 °C). There was no significant difference between these two groups with respect to BMI (26.2 ± 7.8 vs. 27.1 ± 1.4 kg/m2), smoking, duration of DM, glycemic status (HbA1c), lipid profile, and prevalence of hypertension, neuropathy, retinopathy, nephropathy, CAD, CVA, or PAD. However, active foot ulcer (67% vs. 22%, $p = 0.03$),

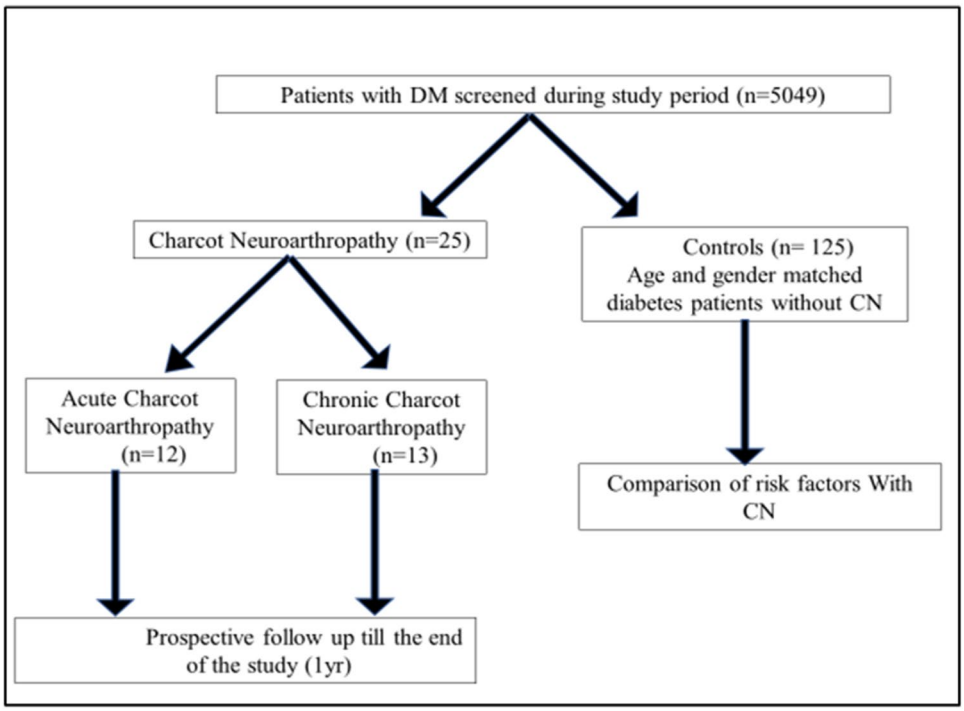


Fig. 1 Overview of study

Table 1 Comparison between CN patients and their controls at baseline

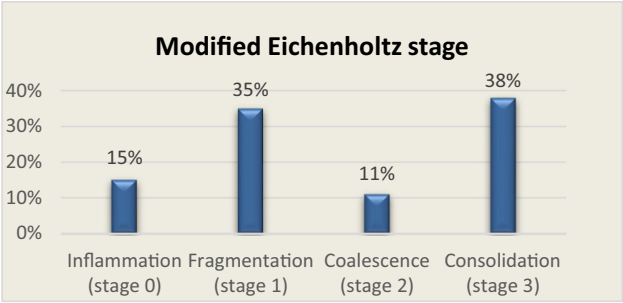
Variable	CN ($n=25$)	Controls ($n=125$)	p-value
Age (years)	55.6 ± 8.8	54.7 ± 8.5	0.84
Gender (males/females)	17/8	85/40	0.90
History of smoking, *n* (%)	8 (32)	36 (29)	0.74
BMI (kg/m^2)	27.9 ± 3.2	26.2 ± 2.7	0.02
Duration of DM (years)	12.0 ± 3.9	9.6 ± 3.5	0.001
FPG (mg/dL)	171 ± 45	154.8 ± 38.4	0.02
2-h PPG (mg/dL)	264.7 ± 17.2	209.2 ± 28.6	0.04
HbA1c (%)	10.3 ± 2.4	8.8 ± 1.9	0.001
Creatinine (mg/dL)	1.1 ± 0.5	1.0 ± 0.5	0.15
eGFR (mL/min/1.73 m^2)	76.9 ± 34.2	84.4 ± 30.9	0.50
UACR (mg/g)	63.8 ± 87.6	38.5 ± 46.9	0.17
Triglycerides (mg/dL)	161 ± 25.4	156.9 ± 33.3	0.63
LDL c (mg/dL)	124.6 ± 19.5	129.7 ± 28.3	0.23
HDL c (mg/dL)	42.2 ± 9.2	43.5 ± 8.8	0.43
Hypertension, *n* (%)	17 (68)	73 (58)	0.37
Neuropathy, *n* (%)	25 (100)	91(73)	0.001
Nephropathy, *n* (%)	5 (20)	16 (13)	0.34
Retinopathy, *n* (%)	17(68)	58 (46)	0.04
ABI	Rt:1.16 ± 0.21 Lt:1.20 ± 0.25	Rt:1.15 ± 0.22 Lt:1.17 ± 0.21	0.86 0.48
PAD, *n* (%)	2 (8)	24 (19)	0.18
CAD, *n* (%)	5 (20)	19 (15)	0.55
CVA, *n* (%)	3 (12)	10 (8)	0.51
On OAD only, *n* (%)	8 (32)	62 (50)	0.10
On insulin only, *n* (%)	11 (44)	43 (34)	0.36
On OAD with insulin, *n* (%)	6 (24)	20 (16)	0.33

CN, Charcot neuroarthropathy; *BMI*, body mass index; *DM*, diabetes mellitus; *FPG*, fasting plasma glucose; *eGFR*, estimated glomerular filtration rate; *UACR*, urinary albumin creatinine ratio; *LDLc*, low density lipoprotein cholesterol; *HDLc*, high density lipoprotein cholesterol; *ABI*, ankle brachial index; *PAD*, peripheral arterial disease; *CAD*, coronary artery disease; *CVA*, cerebrovascular accident; *OAD*, oral antidiabetic medication

clawing of toes (92% vs. 31%, $p=0.02$), and Rocker bottom feet deformity (77% vs. 8%, $p<0.001$) were significantly more common in CCN compared to ACN.

Radiological findings in CN patients

Of the 25 patients with CN, the right foot was involved in 14 patients and the left foot was involved in 10 patients and, in one patient, both feet were involved (total of 26 Charcot feet in 25 patients). Staging of CN according to Eichenholtz is given in Fig. 2. Out of 12 ACN patients, three patients were detected to be in Eichenholtz stage 0



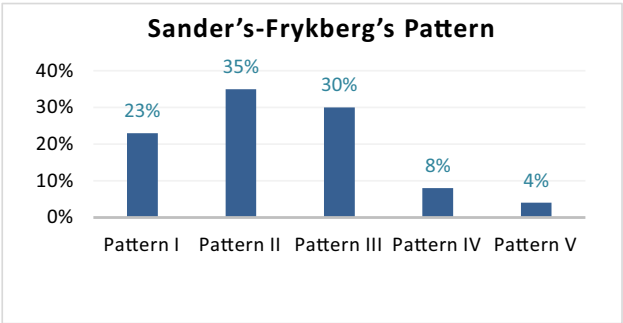


Fig. 2 Pattern of involvement of foot in CN patients

(one had bilateral feet involvement) and nine patients were in stage 1. Out of 13 CCN patients, three patients were detected to be in Eichenholtz stage 2 and 10 patients were in stage 3 (Fig. 3).

The pattern of involvement of joints in the foot in the present study according to Sanders and Fryberg classification (Fig. 2) shows pattern II (TMT joints) was the most common (35%) followed by pattern III (intertarsal joints, 30%) followed by pattern I (MTP and IP joints, 23%). Least involved was pattern V (calcaneum) (4%). In three patients, standard X-rays could not detect ACN with clinical features of inflammation was picked by MRI. Meary's angle was increased in 65% (17 feet), calcaneal pitch was decreased in 50% (13 feet), and cuboid height was decreased in 58% (15 feet) of all CN patients.

MRI findings

MRI foot was done in all cases of CN. Patients with Eichenholtz stage 0 ACN had bone marrow oedema and soft tissue oedema in sagittal STIR sequence. In the present study, three patients who were in stage 0 with normal X-ray findings were detected by MRI with bone marrow oedema. MRI findings in feet, which were in stage of fragmentation, were bony destruction with cortical fractures and dislocations with bone marrow oedema and soft tissue oedema in STIR sequence. MRI findings of CCN (Eichenholtz stages 2 and 3) were fractures, dislocations, with subchondral cysts with

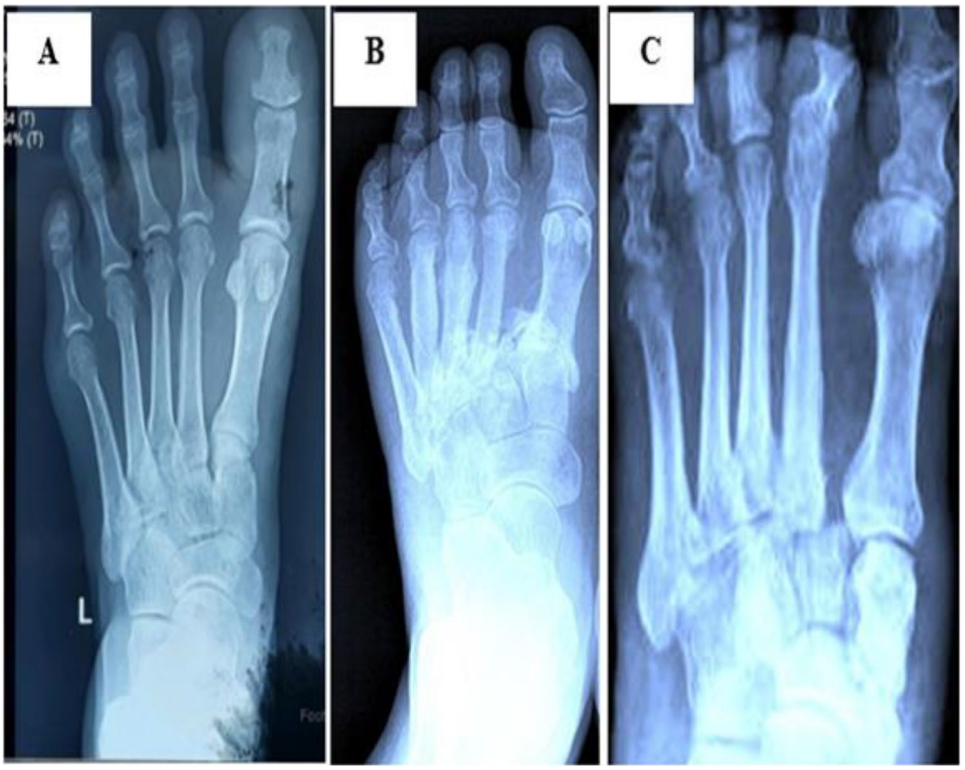


Fig. 3 **A** Radiograph of the left foot AP view showing no abnormalities (stage 0); **B** lateral subluxation of 2nd to 5th metatarsal bases with fracture at the base of 2nd metatarsal and dislocation of medial Lisfranc joint and obliteration of Lisfranc joint space (stage 1); **C** fusion and coalescence of larger fragments and sclerosis of bones (stage 2)

intraarticular bodies with gross deformity of feet without bone marrow oedema in STIR sequences. Two patients of CCN had osteomyelitis, which was detected by MRI by the ghost sign (bones that disappear on T1-weighted images and reappear after contrast or on T2W images).

Comparison of systemic inflammatory parameters in acute and chronic CN at baseline

To look for the systemic inflammation, CRP, ESR, and TLC were done in cases of CN. Patients with ACN had significantly higher median (IQR) CRP compared to patients with CCN [21 mg/L (IQR 15.5–26) vs. 8 mg/L (IQR 5–9); $p=0.04$]. There were no statistically significant differences with respect to ESR and TLC between acute and chronic CN patients.

Follow-up of CN patients

Follow-up of acute CN patients

The median duration of follow-up in the ACN patients after clinical resolution was 4 months (IQR 3.5–4.7 months), and the total duration of follow-up was 7.7 months (IQR 6–9.7 months). At the end of the study, 11 out of 13 Charcot feet had complete clinical resolution, two were in follow-up as they were not in clinical resolution. These two patients had fragmentation and dislocation (Eichenholtz stage 1) and did not comply with the offloading protocol. The median duration for complete clinical resolution in patients with acute CN was 3 months [IQR 2.5–4.5 months]. Depending on the location of arthropathy, healing time in TCC varied. The median duration for clinical resolution for forefoot arthropathy was 2.5 months (IQR 2–3 months), and for midfoot and hindfoot arthropathies, it was 4 months (IQR 3–4.5 months) and 6 months, respectively. There was no statistically significant difference in the median duration of clinical resolution for Eichenholtz stage 0 and stage 1 [3 (IQR 2–4.5) months vs. 4 (IQR 3–6) months; $p=0.25$] in all regions**.** On follow-up of ACN patients at the time of clinical resolution, there was a significant decrease in FPG, 2-h PPG, HbA1c, and inflammatory markers (ESR, CRP) from the baseline.

Follow-up of chronic CN patients

The median duration of follow-up in CCN patients was 6 months (IQR 4–8.7). Of the 13 patients with CCN, six had ulcers at the time of initial diagnosis. On follow-up with customized footwear and appropriate therapy, all the patients had healing of ulcers with a median duration of 1.5 months. For the seven patients who had no ulcers at the time of diagnosis with proper customized footwear, none of them developed new ulcers at the end of the study. At the end of the study, there was a significant decrease in FPG, 2-h PPG, and HbA1c, but inflammatory markers showed no significant difference from baseline.

Limitations of the study

The present study was a single-centre study, and the duration of the study was short. We have not matched duration of diabetes for selection of controls. Inflammatory cytokines like TNF-α, IL-6 have not been measured in our study. X-ray of foot was not done on follow-up of CN patients as none had progression of foot deformity. Bone turnover markers and bone mineral density were not assessed in the present study.

Discussion

In the present study, diabetic CN was found to be present in 0.49% of diabetic patients in the fifth to sixth decades of life with bilateral foot involvement in only 4% of patients. There was a wide variation in the prevalence of diabetic CN reported earlier, varying from 0.08 to 35% [13, 14]. These variations in prevalence of CN may be attributed to the lack of uniform criteria for the diagnosis of CN and inclusion of various high-risk groups of patients in those studies. There was also conflicting data on bilateral foot involvement in previous studies, varying from 9 to 75% [15–17].

Diabetic patients developing CN had higher BMI, poor glycemic control, longer duration of DM, and higher prevalence of neuropathy and retinopathy complications. Obesity was implicated as a risk factor for diabetic CN by increasing the biomechanical load on a deranged foot. In a study by Stuck et al., obesity alone increased the risk of CN by 59% [18]. The poor glycemic control and long duration of DM increase the risk of neuropathy and risk of repeated microtrauma, which go unnoticed. The present study also showed 42% of patients had history of trauma prior to CN. This corroborates to the neurotraumatic theory [19] in the pathogenesis of diabetic CN.

ACN and CCN were defined clinically by inflammatory signs and radiologically by Eichenholtz staging. As expected, the inflammatory signs were present in all cases of ACN and absent in all cases of CCN. However, clawing of toes, rocker bottom feet, anhidrosis, and callosities were more common in CCN patients. The development of these complications could be due to autonomic neuropathy and motor involvement in these patients.

Radiological diagnosis of CN is the cornerstone in the diagnosis and management of CN. The most common involvement among foot bones was midfoot (65%) (Sanders and Frykberg's patterns II and III) followed by forefoot (23%) (Sanders and Frykberg's pattern I), and the least common was the hindfoot (12%). The present study is in concordance with previous studies where midfoot was the commonest site of involvement [7, 20, 21]. Increased Meary's angle and decreased calcaneal pitch and decreased cuboid height were found in 68%, 50%, and 58% of CN patients, respectively, in the present study. The measurement of these angles helps in assessing the progression of disease. However, X-rays were non diagnostic in very early ACN (Eichenholtz stage 0), which were picked by MRI foot as seen by various other studies [7, 22].

MRI is useful as a diagnostic modality in most of the cases of CN. MRI could be able to detect four feet (3 patients, 25% of ACN), which were missed by X-rays. In these early cases (Eichenholtz stage 0), bone marrow oedema as identified by STIR images is a useful tool. MRI is also useful in assessing the progression of disease and identifying osteomyelitis. In the present study, two CCN patients had osteomyelitis, which were identified by MRI by the ghost sign.

The main stay of treatment in patients with ACN is immobilization with TCC. Understanding the duration of healing time is important in managing diabetic CN. The median duration of healing in ACN patients was 90 days (IQR 75–135 days). Depending on the location of arthropathy, healing time in TCC varied. This is useful while managing CN, affecting various regions of foot. Our finding is shorter than reports from studies in UK (median, 9 to 12 months) [23, 24] but is almost comparable to studies from USA (mean, 3 to 5 months) [25, 26] and other Asian countries (median, 5 months) [27]. This variation may be due to differing patient characteristics, patterns and staging of CN, definition used for Charcot resolution, type of offloading techniques used and adherence to offloading, experience in applying the TCC, protocols for monitoring Charcot progression, and study design [28]. The main concern in patients with CCN is to prevent progression of deformities, formation of new ulcers, and osteomyelitis. Only 2 patients had osteomyelitis at initial presentation, but none developed during follow-up.

Conclusions

The present study highlights that CN in DM patients are not uncommon complication. DM patients having poor glycemic control and longer duration of DM are at risk of developing CN. MRI is helpful in detecting early cases of CN, which may be missed on X-ray. Early diagnosis and appropriate offloading lead to clinical remission in majority of ACN and healing as well as prevention of foot ulceration in CCN.

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Data Availability Data is available through the corresponding author upon justified request.

Declarations

Ethics approval Ethical clearance was taken from the institutional ethics committee with registration no.783/ Chairman- IEC, M.K.C.G. Medical College, Brahmapur-4.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflicts of interest The authors have no conflicts of interest.

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