Role of bisphosphonates in the management of acute Charcot foot

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Abstract

Diabetes mellitus is the most common cause of Charcot neuropathy affecting foot and ankle. Acute Charcot foot (CF) presents with a red and swollen foot in contrast to the painless deformed one of chronic CF. Enhanced osteoclastogenesis plays a central role in the pathogenesis of acute CF. Many studies have shown elevated levels of bone turnover markers in patients with acute CF confirming it. These findings have led clinicians to use anti-resorptive agents [bisphosphonates (BP), calcitonin, and denosumab] along with immobilization and offloading in acute CF patients. The maximum evidence among all anti-resorptive agents is available for BPs, although its quality is low. Pamidronate has been shown to reduce the markers of activity of CF like raised skin temperature, pain, edema, and bone turnover markers in the majority of studies. Intravenous BPs are known to cause acute phase reactions leading to flu-like illness following their first infusion, which can be ameliorated by oral acetaminophen. Alendronate is the only oral BP used in these patients. It needs to be taken on an empty stomach with a full glass of water to avoid esophagitis. The side-effects and contraindications to BPs should be kept in mind while treating acute CF patients with them.

Key words: Charcot foot; Diabetes mellitus; Charcot neuroarthropathy; Bisphosphonates; Pamidronate

Core tip: Bisphosphonate is an attractive treatment option for acute Charcot foot. This is based on the fact that increased osteoclastic activity plays a central role in the pathogenesis of acute Charcot foot. Among bisphosphonates, the maximum evidence in the literature is available for pamidronate. It has been shown to reduce the markers of Charcot foot activity, like raised skin temperature, pain, and edema. However, the quality of evidence is low. They should be used along

with immobilization and offloading. The side effects of bisphosphonates and their contra-indications for use should be kept in mind while treating these patients with them.

INTRODUCTION

Charcot foot (CF), also quoted as Charcot neuroarthropathy (CN), derives its name from Jean-Martin Charcot, who in 1868 first described neuroarthropathic changes in patients with tabes dorsalis[1]. It was not until 68 years later, in 1936, that William Riley Jordan first established the association between diabetes mellitus (DM) and painless neuropathic arthropathy of ankle[2]. It is a rare and devastating condition leading to the destruction of bone and joints and culminating in fractures, dislocations, deformities, and amputation of the foot in neglected cases. Virtually any condition that causes neuropathy can lead to CF, such as DM, syphilis, leprosy, spinal cord injury, meningomyelocele, syringomyelia, chronic alcoholism, and a host of other conditions like psoriasis, sarcoidosis, rheumatoid arthritis, human immunodeficiency virus, and Parkinson's disease. Currently, the world is witnessing an exponential rise in the prevalence of DM and its complications. According to the World Health Organization 2016 report, around 422 million people are living with DM[3]. This has made DM the most common cause of CN affecting foot and ankle. The incidence of CF in diabetic patients ranges between 0.1% and 7.5%[4].

Today, the pathophysiology of CF is still a bone of contention even after one and half centuries since its first description. Conventional theories for it include the neurovascular theory postulated by Charcot himself and the neurotraumatic theory proposed by Volkmann and Virchow[5]. Peripheral sensorimotor neuropathy along with autonomic dysfunction is the essential factor for the development of CN. Usually a trivial trauma in the insensate foot kicks off the inflammatory cascade. Not all neuropathic patients, however, develop CF.

Recent advancements in the understanding of the pathophysiology of CF has shed light on factors like inflammatory cytokines and their interaction with receptor activator of nuclear factor kappa-B (RANK), its ligand (RANKL), and osteoprotegerin (OPG)[6]. Longstanding hyperglycemia, with its complications ranging from neuropathy to formation of advanced glycation end products (AGEs)[7] and protein kinase C (PKC) activation[8], is the major culprit. Calcitonin gene-related peptide (CGRP)[9], Wnt/beta-catenin pathway[10], and OPG gene polymorphisms[11] are new players in the field.

Interaction between RANKL, nuclear factor kappa-B (NF-κB), and pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), Interleukin-1β (IL-1β), and interleukin-6 (IL-6) lead to localized osteolysis that destroys bone structure[12]. Moreover, DM patients have lower $1,25(OH)_2D_3$ levels, leading to poor mineralization of bone[13]. Lower calcium levels can stimulate parathyroid hormone, thus contributing to bone resorption and osteopenia[14].

Studies have shown increased levels of osteoclastic resorption markers, such as serum carboxyterminal telopeptide of type 1 collagen (1CTP), in patients with CF[15]. Immobilization and avoidance of physical stress by complete offloading with the help of total contact cast (TCC) is the mainstay in the management of CF[16]. However, because of increased osteoclastic activity, the bone destruction continues unabated. Lower limb osteopenia seen in patients with CN along with increased bone resorptive markers make anti-resorptive agents like bisphosphonates (BPs), calcitonin, and denosumab reasonable treatment options, at least for adjuvant purposes. BPs are pyrophosphate (PP) analogs that have been in medical use for around half a century. First generation BPs like etidronate and clodronate have non-nitrogen containing side chains, whereas second and third generation ones like pamidronate, alendronate, ibandronate, risedronate, and zoledronate have nitrogen containing side chains. Nitrogen containing BPs are much more potent than the first generation ones and work by inhibiting farnesyl PP (FPP) synthase in the mevalonate pathway, which is crucial for function and survival of osteoclasts[17]. In this study, we reviewed the available literature on the use of BPs in patients with acute CF.

CLINICAL PRESENTATION

Clinically, CF can present either in acute or chronic stage, and its features vary according to the stage of presentation. A high index of suspicion is required to diagnose CF in its early stage. Acute CF presents with a red and swollen foot, which is warmer than the contralateral normal foot. Patients may have mild to moderate pain or discomfort at this stage, which is much less when compared to those with a similar degree of inflammation without neuropathy[16,18]. Skin temperature difference of $\geqslant 4°$ Fahrenheit (or $2°$ Celsius) between affected and the normal foot indicates active CF[19]. This can be measured using an infrared thermometer at the maximum point of deformity on the affected foot and at the same point on the normal foot. It is also helpful in monitoring the course of CF. Peripheral pedal pulses are typically bounding because of underlying autonomic neuropathy. Clinical presentation at this stage mimics those of deep vein thrombosis, acute gout, and cellulitis, and the diagnostic dilemma is compounded by the inability of radiographs to detect and differentiate these abnormalities. Magnetic resonance imaging can be helpful at an early stage of disease[20]. If treatment is not

provided at this stage, it leads to further destruction of bone resulting in irreversible damage. Chronic CF is characterized by resolution of inflammation and establishment of residual deformity. Rocker bottom deformity is the classic abnormality that arises due to collapse of plantar arch in mid foot[21]. This results in abnormal high pressure areas on the weight bearing sites of the plantar surface, making it prone to ulceration[22].

PATHOGENESIS OF ACUTE CHARCOT FOOT

Conventional theories

Two age-old theories pertaining to the pathogenesis of CF that are still pertinent include neurovascular theory and neurotraumatic theory. Neurovascular theory[1] suggests that damage to trophic or vasomotor nerves secondary to the underlying condition results in failure of vasoregulation, causing opening of arteriovenous shunts. This leads to the increased supply of blood to the bone, resulting in greater flux of monocytes and osteoclasts and culminating in bone resorption. Other factors, like peripheral vascular disease, are expected to co-exist with diabetic neuropathy. This leads to decreased blood flow to lower limbs, which can act as a protective factor against CF[23]. This probably explains why CF affects only a fraction of DM patients with neuropathy.

On the other hand, Volkmann and Virchow in their neurotraumatic theory suggested that trauma to the insensate foot leads to CN[5]. Repeated microtrauma in a patient with sensory neuropathy leads to bone destruction and deformity. Though both feet of susceptible patients have the propensity to develop CF, only the one exposed to recurrent trauma develops CF. This provides some ground for the pathogenesis of unilateral CF in the background of generalized neuropathy. However, it has been found to be bilateral in 9% to 39% of cases[24]. With the passage of time, we have now come to know that CF results from the combination of these processes. Autonomic neuropathy weakens the bone because of increased blood supply, whereas sensory neuropathy causes loss of protective sensation leading to unperceived recurrent trauma to the abnormal bone. Muscle weakness due to motor neuropathy adds fuel to the fire, leading to joint instability and abnormal plantar pressures[25]. These progress later to bone fracture and dislocation in foot and ankle.

Other factors that play a role in the pathogenesis of CF are: (1) inflammatory cytokines; (2) AGEs; and (3) neuropeptides and inorganic molecules. These mediators finally stimulate osteoclastogenesis, leading to bone loss *via* RANKL/OPG pathway (Figure 1).

Role of inflammatory cytokines

In addition to his neurovascular theory, Charcot recognized inflammation as one of the contributors to CN. Christensen *et al*[26] in their study showed that hyperemia during an acute attack of CF was most likely secondary to the inflammation rather than sympathetic neuropathy. Thus, it is unabated inflammation in the background of neuropathy that results in the imbalance between osteoclasts and osteoblasts leading to bone resorption. This pro-inflammatory state can be triggered by repeated microtrauma. Hyperglycemia in DM can lead to increased PKC activity and formation of AGEs along with decreased phosphatidylinositol 3 kinase activity[8]. This, in turn, results in an excessive production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. This storm of pro-inflammatory cytokines disturbs osteoclast-osteoblast homeostasis. Baumhauer *et al*[12] histologically examined 20 tissue biopsy specimens obtained from patients with CF. Immunohistochemical study of each of these biopsies showed positivity for IL-1, IL-6, and TNF-α. This was conclusive of stimulation of osteoclastic progenitor cells, leading to osteoclastogenesis by the cytokines present in the background during acute and reparative stages of CF. But inflammatory cytokines alone do not directly account for the increased osteoclastogenesis. Jeffcoate *et al*[27] suggested that inflammatory cytokines lead to increased osteoclastogenesis *via* increased expression of NF-κB. This results in bone destruction, which again potentiates the inflammatory response thus culminating in a vicious cycle[27]. Increased cytokines lead to increased activity of RANKL that in turn activates RANK, which is expressed on osteoclast precursors. Increased RANK stimulates intracellular pathways, leading to increased formation of NF-κB. NF-κB stimulates differentiation of osteoclast premature cells to mature osteoclasts, culminating in increased osteoclastic activity. Simultaneously, NF-κB up regulates expression of OPG, a decoy receptor for RANKL, which effectively antagonizes its activity[28]. Ndip *et al*[29] in their study showed that patients with CN have elevated RANKL/OPG ratio and illustrated that abnormal RANKL/OPG signaling plays a crucial role in increased osteoclastic bone resorption. Another bone regulating pathway involving Wnt/β-catenin has been speculated to have some role in bone remodeling in patients with CF[10]. To date, the RANKL/OPG pathway defect remains the most accepted theory.

Role of hyperglycemia

Glycation of collagen occurs normally with aging[30]. Hyperglycemia accelerates this process of non-enzymatic glycation, leading to the formation of Amadori products. These products combine with amino groups on other protein molecules, ending up in formation of the AGEs, which are known to play a major role in various complications of diabetes[31]. AGEs cause irreversible posttranslational modification of proteins, thus rendering them defective. Binding of AGEs to their receptor (RAGE) stimulates nicotinamide adenine dinucleotide phosphate oxidase[32], resulting in the production of reactive oxygen
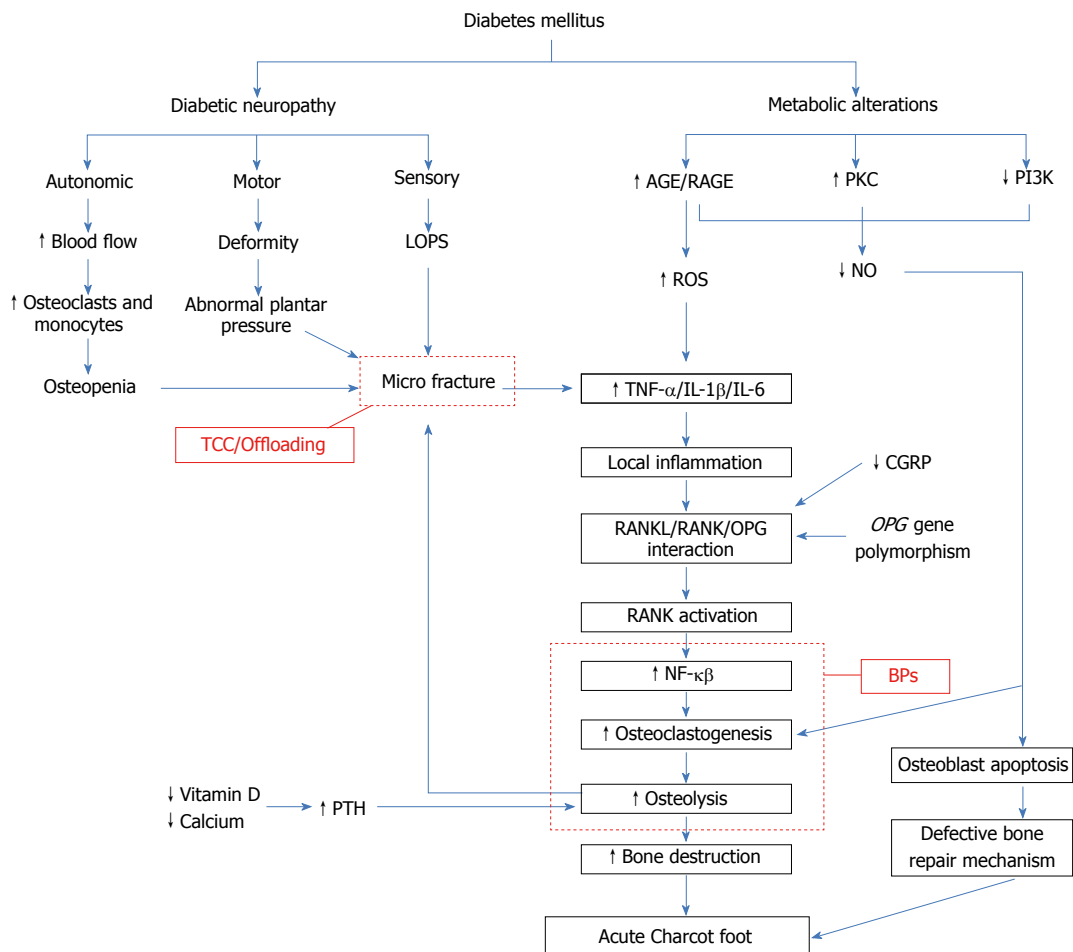
Figure 1 Pathogenesis leading to acute Charcot foot. AGE: Advanced glycation end products; RAGE: Receptor of AGE; PKC: Protein kinase C; PI3K: Phosphatidylinositol 3 kinase; LOPS: Loss of pain sensation; ROS: Reactive oxygen species; NO: Nitric oxide; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; TCC: Total contact cast; CGRP: Calcitonin gene related peptide; NF-κβ: Nuclear factor κβ; RANKL: Receptor activator of NF-κβ ligand; OPG: Osteoprotegerin; BP: Bisphosphonates; PTH: Parathyroid hormone.

species and subsequently increased expression of NF-κB[33]. Katayama *et al*[34] elucidated the effects of AGE-modified collagen on differentiation and function of the osteoblastic cell *in vitro* and suggested that the same changes may lead to osteopenia in diabetic patients. AGEs prevent differentiation of human mesenchymal stem cells[35]. They stimulate apoptosis of osteoblasts through mitogen activated protein kinase and cytosolic apoptotic pathways that are independent of NF-κB activation[36]. AGEs also cause endothelial dysfunction by extinguishing nitric oxide (NO) activity[37]. Soluble RAGE (sRAGE) is a C-terminal splice variant of RAGE and has been shown to be cytoprotective against AGE[38]. Witzke and colleagues in their cross-sectional study concluded that patients with CN had lower levels of sRAGE compared to healthy controls and diabetic patients without CN[7]. They also demonstrated a positive correlation between sRAGE levels and calcaneal bone stiffness suggesting that sRAGE has a protective effect against bone resorption and loss of sRAGE defense may be one of the factors leading to CN. Thus, AGEs lead to increased osteoclastogenesis *via* the RANKL/NF-κB pathway and decreased bone formation by their action on osteoblasts through multiple pathways.

Role of neuropeptides and inorganic molecules
Research has shown that feedback mechanisms are abnormal in patients with DM, leading to increased expression of RANKL. One such mechanism involves CGRP secreted from the healthy neurons. It antagonizes RANKL expression by increasing the release of anti-inflammatory cytokines like IL-10[14]. This leads to inhibition of osteoclastogenesis. The release of CGRP is reduced in peripheral and autonomic neuropathy, leading to continuous unchecked RANKL activity[39]. NO is an inorganic molecule that plays a role in CN. AGEs, along with increased PKC expression and decreased phosphatidylinositol 3 kinase activity, results in decreased production of NO. Studies have shown that decreased NO levels can stimulate osteoclastogenesis, thereby leading to bone resorption[40]. Endothelial NO synthase (eNOS) also regulates osteoblast proliferation and function[41,42]. eNOS knockout animals have been shown to develop osteoporosis secondary to defective

bone formation[42]. Both these molecules were studied by La Fontaine and colleagues in their study[9]. They performed immunohistological analysis of bone specimens from three groups of patients with DM: group 1 included healthy patients without neuropathy, group 2 included those with neuropathy, and group 3 included those with CN stage Ⅱ or Ⅲ. They observed decreased levels of CGRP in patients in groups 2 and 3 when compared to group 1. They also found a statistically significant difference in the levels of eNOS, with highest levels in healthy DM patients without neuropathy (group 1) and lowest levels in DM patients with CN (group 3).

ROLE OF ANTIRESORPTIVE THERAPY IN ACUTE CHARCOT FOOT

Increased osteoclastic activity is the essence of pathogenesis leading to CF. Many studies have shown elevated levels of bone turnover markers (BTMs) in patients with acute CF pointing towards this fact.

Gough *et al*[15] compared BTMs between four groups of patients: acute CF, chronic CF, diabetic controls, and non-diabetic controls. They concluded that levels of serum 1CTP were significantly elevated in patients with acute CF as compared to the other three groups ($P < 0.0001$). Jostel *et al*[43] in their review mentioned similar results with urinary cross linked N-telopeptides of type 1 collagen, pointing towards accelerated collagen breakdown in these patients. However, levels of serum procollagen type Ⅰ carboxy-terminal propeptide did not show intergroup differences.

These findings have forced researchers to use antiresorptive agents along with traditional immobilization in acute CF patients. To date, agents like BPs have been used in multiple studies (discussed later). BPs are the principal agents in the pharmacological armamentarium against diseases, where the osteoblast-osteoclast imbalance is the underlying pathology. They are analogues of inorganic PP binding to hydroxyapatite crystals, which have extremely high affinity for bone mineral. They get deposited in mineralized bone matrix and are released at the time of bone resorption. This high affinity for bone mineral and resultant uptake by activated osteoclasts at the time of resorption ensures its toxic accumulation only in osteoclasts. First generation non-nitrogen containing BPs are metabolized to cytotoxic adenosine triphosphate analogues by osteoclasts. Intracellular deposition of these toxic non-hydrolyzable analogues causes apoptosis of osteoclasts[44]. Unlike their predecessors, second and third generation BPs like alendronate, pamidronate, ibandronate, risedronate, and zoledronate have nitrogen side chain bound to the central carbon, which magnifies their potency manifolds. The mechanism by which nitrogen containing BPs impacts osteoclast activity and survival differs from that of the first generation BPs. After getting internalized, they inhibit FPP synthase, a key enzyme in the mevalonate pathway, which is responsible for

production of cholesterol and isoprenoid lipids[45]. As a result, isoprenylation of guanosine triphosphate binding proteins like Ras, Rho, and Rac is inhibited[46]. These signaling proteins are important for the regulation of cell survival, proliferation, and cytoskeletal organization. Of particular importance among these is inhibition of protein prenylation and Ras signaling within osteoclasts, resulting in defective intracellular vesicle transport[47]. Thus, osteoclasts fail to form ruffled borders, which are necessary for resorption of bone. In addition to this, FPP synthase inhibition leads to an increase in isopentenyl diphosphonate, which is further metabolized to triphosphoric acid 1-adenosin-5′-yl ester 3-[3-methylbut-3-enyl] ester, also known as ApppI. Intracellular accumulation of this ATP analogue leads to apoptosis of osteoclasts (Figure 2). Potency of BPs is decided based on the inhibition of FPP synthase activity. In this respect, zoledronate is the most potent BP followed by risedronate, ibandronate, alendronate, and pamidronate with decreasing potency[17]. Moreover, in animal studies, BPs have shown to possess anti-nociceptive effects that can contribute to pain relief in patients with acute CF[48,49].

Other anti-resorptive agents like calcitonin and denosumab have been successfully used in past. Calcitonin is a polypeptide secreted from parafollicular C cells of the thyroid. It inhibits bone resorption by its direct action on the osteoclast calcitonin receptor[50]. Its quick action leads to loss of ruffled border of osteoclasts and decreased number of osteoclasts. It inhibits cytoplasmic motility and generates pseudopodial retraction in osteoclasts[51]. It prevents the production and release of tartrate-resistant acid phosphatase by osteoclasts[52]. It has also been shown that calcitonin may inhibit apoptosis of osteocytes and osteoblasts[53]. To evaluate the effects of calcitonin on disease activity, Bem *et al*[54] conducted a randomized controlled trial on the effectiveness of intranasal salmon calcitonin 200 IU daily in 32 diabetic patients with acute CF. One group received intra-nasal salmon calcitonin 200 IU daily and calcium supplementation, while the other got only calcium supplements. All patients were offloaded using removable devices. Skin temperature and BTMs (measured monthly for first 3 mo and then at 6 mo) were used for monitoring the course of treatment. Nine patients with renal insufficiency, *i.e.,* serum creatinine > 120 μmol/L, were also included. Skin temperature reduced significantly at 3 mo without much inter-group difference. Significant reduction was noted in levels of 1CTP in the treatment group at 3 mo as compared to control group ($P < 0.01$). A similar trend was observed for bone-specific alkaline phosphatase (ALP) at 3 mo ($P < 0.05$), but the intergroup difference disappeared at 6 mo. The authors concluded that intranasal calcitonin not only reduces bone resorption and prevents progression of acute CF but also can be effective in patients with renal insufficiency. Calcitonin also has analgesic action mediated through central as well as peripheral mechanisms[55,56].
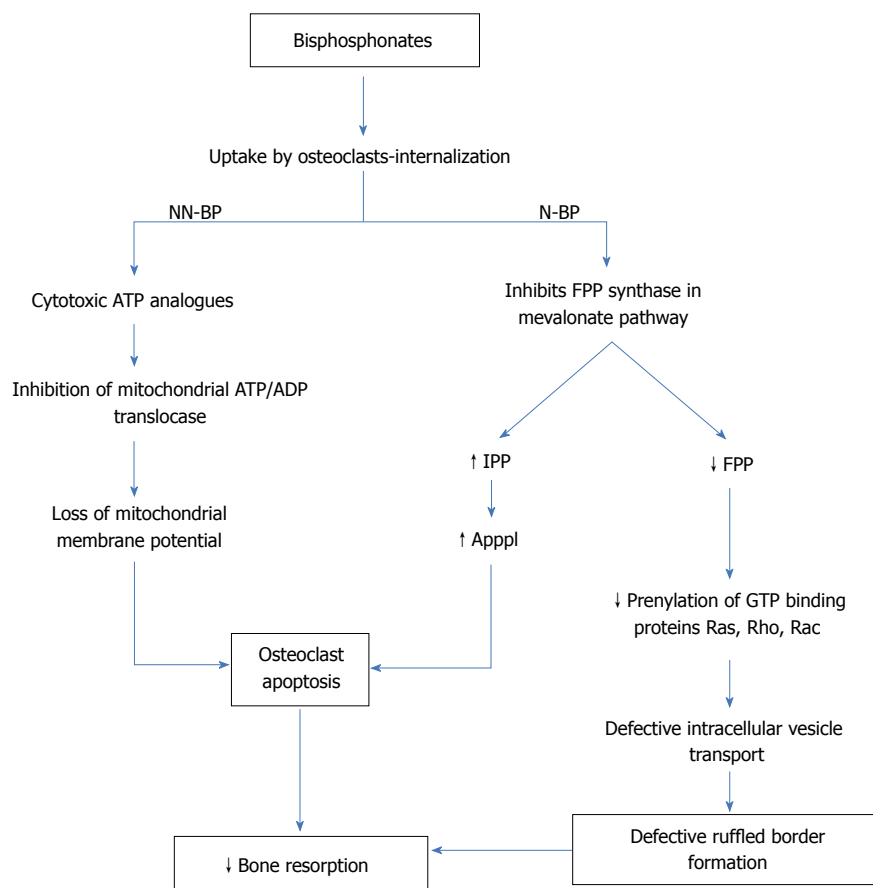
Figure 2 Molecular mechanisms of bisphosphonates. NN-BP: Non-nitrogen containing bisphosphonates; N-BP: Nitrogen containing bisphosphonates; FPP: Farnesyl pyrophosphate; IPP: Isopentenyl diphosphonate; Apppl: Triphosphoric acid 1-adenosin-5'-yl ester 3-[3-methylbut-3-enyl]ester.

As RANKL activation plays a major role in the pathogenesis of acute CF, its inhibition can be an attractive treatment option. Denosumab is a fully human monoclonal antibody that targets RANKL. It prevents interaction between RANKL and its receptor RANK. This leads to inhibition of RANKL, which in turn prevents differentiation of osteoclast precursors to mature multinucleated osteoclasts. The basic difference between BPs and denosumab is that the former act after getting internalized, while the latter works in an extracellular environment[57]. It has been shown to reduce osteoporosis-related fracture[58]. Taking cues from this work, Busch-Westbroek *et al*[59] performed an observational study to evaluate effects of denosumab in patients with acute CF. Patients seen between 2012 and 2014 were included as controls, and those from 2014 to 2016 were subjected to single subcutaneous injection of 60 mg denosumab. All the patients from 2012 to 2016 were immobilized using TCC and were supplemented with calcium and vitamin D. Fracture resolution time, as judged on radiographs and time to clinical cessation based on usage of TCC, were compared between the two groups. Both parameters were significantly shorter in the group receiving denosumab ($P < 0.01$). TCC was used until resolution of edema, and skin temperature difference between both feet decreased to less than 2℃ in this study.

EVIDENCE OF BISPHOSPHONATE USE IN ACUTE CHARCOT FOOT

Case reports and case series
In 1994, Selby *et al*[60] first reported use of intravenous (IV) pamidronate in six diabetic patients with acute CF. Patients were treated with infusion of 30 mg of pamidronate followed by five infusions of 60 mg every 2 wk. Skin temperature, as a marker of disease activity, was monitored by an infrared thermometer. All patients reported marked improvement in their mobility and reduction in pain and swelling. Skin temperature difference between the affected and normal foot reduced from 3.4 ± 0.7 ℃ to 1.0 ± 0.5 ℃ ($P = 0.05$). Serum ALP, which was used as BTM, was also significantly reduced (by 25 ± 3%, $P < 0.001$).

In 1999, Young MJ[61] reported two diabetic patients with CF who were treated with IV infusion of 30 mg of pamidronate followed by two infusions of 60 mg every 2 wk along with immobilization measures. In both patients, skin temperature difference normalized (*i.e.*, < 2 ℃), edema and pain subsided after 3 mo, and there was no deformity in the lower limbs.

In 2002, Yu *et al*[62] reported a case of recurrent CF in a 55-year-old diabetic patient. He was treated with serial Jones compression bandages followed by non-

weight bearing brace with a removable pneumatic walker along with three IV infusions of pamidronate each 2 wk apart. The patient improved clinically, swelling disappeared, and he resumed full weight bearing with an ankle-foot orthosis.

In 2002, Pakarinen *et al*[63] retrospectively studied 36 CF in 32 diabetic patients. Eighteen cases received IV pamidronate 30 to 60 mg once a wk for 6 wk. They did not find any difference in casting time between patients who received pamidronate and those who did not (11 wk *vs* 13 wk). There was no information regarding criteria used for removal of casts or the indication for BP use in a particular patient. This along with non-uniformity in the timing of cast usage make it difficult to analyze the results of this study.

In 2007, Moreno *et al*[64] prospectively analyzed the efficacy of pamidronate over 12 mo in four diabetic patients with acute CF. Treatment protocol comprised of three IV infusions of pamidronate each 2 mo apart. The dose used was 60 mg in patients with weight < 70 kilograms and 90 mg in patients with weight > 70 kilograms. Clinical examination, radiographs, and urine BTMs were done before and 12 mo after treatment in all patients. All patients exhibited significant clinical improvement. Urinary BTMs showed a statistically significant reduction. All patients had radiological improvement.

In 2008, Naqvi *et al*[65] reported three diabetic patients with acute CF. First patient, a 54-year-old female was treated with three IV infusions of 90 mg of pamidronate every 2 mo. After the first infusion, the patient had marked clinical improvement in swelling, pain, erythema, and warmth. Following the second infusion, she was able to bear weight on her foot, and after the last infusion she was ambulant without the walker. The second patient was a 49-year-old African-American female, who was treated with single IV infusion of 60 mg pamidronate along with walking cast and physiotherapy. At 6 and 9 mo follow-ups, signs of inflammation disappeared. Although the natural arch of the foot was lost, she was able to walk with a boot. The third patient was an 82-year-old white woman, who was treated with a single 90 mg of pamidronate infusion. This led to significant clinical improvement, and she was able to walk with the boot at 4 wk of follow-up. One year later, she had no symptoms and was able to walk normally.

In 2002, Rajbhandari *et al*[23] in their review revealed their anecdotal experience in patients with acute CF. They noted significant symptom relief in these patients with two IV infusions of 90 mg pamidronate.

Observational studies
In 2004, Anderson *et al*[66] retrospectively evaluated 33 patients of acute CF who were diagnosed between October 1997 and January 2001. These patients were divided in two study groups - group 1 comprising of 18 patients who received IV pamidronate (60 to 90 mg) and group 2 comprising of 15 patients who did not receive any BPs. Both groups received standard immobilization measures. Finally, after excluding five patients each from groups 1 and 2 due to either lack of consent for treatment or bilateral CF or association with some other bone disease or infection, 13 patients from group 1 and 10 patients from group 2 were analyzed. In group 1 patients, limb temperature decreased by 2.8 °F at 48 h and 7.4 °F at 2 wk, whereas group 2 showed no reduction in temperature at 48 h and a reduction of 2.3 °F at 2 wk. The same trend was seen in serum ALP, which plummeted by 53% at 2 wk in group 1 and showed a meager reduction of 9% in group 2. Thus, this study demonstrated a statistically significant reduction in skin temperature and serum ALP in patients treated with pamidronate.

In the largest web-based observational study published in 2012, Game *et al*[67] surveyed 288 diabetic patients with acute CF from 76 centers across the United Kingdom and Ireland. At baseline, 35% of the subjects were offloaded with the non-removable devices, while 50% were offloaded using the removable devices. Only 25% of patients received IV BPs, and around 20% received oral BPs. Follow-up data regarding resolution was available in 219 patients. The resolution was defined as a time-point when the patient starts walking in either normal or orthotic footwear. For those who received BPs, median resolution time was significantly longer than patients not receiving it (12 mo *vs* 10 mo, *P* = 0.005). Resolution time was significantly more in both groups as compared to other studies. One of the reasons for this can be the definition of resolution used, which required the patient to be ambulant. Regarding prolongation of resolution time with BPs, the authors have speculated the following possible explanations: first, BPs may have been used only in patients who had more severe CF or in non-responders to offloading alone. Second, BPs must have been used only if the non-removable device was unavailable. It is very tough to infer much from the results provided by this study. No data were provided regarding skin temperature or any BTMs or the type of BP used.

In 2013, Bharath *et al*[68] were the first to compare the effects of two BPs in a prospective randomized comparative study of 45 type 2 diabetic patients with acute CF. Patients were randomized into two groups, Z and A receiving a single IV infusion of 5 mg zoledronate (diluted in 100 mL normal saline over 30 min) and oral alendronate 70 mg once weekly, respectively, until resolution of the disease. The complete clinical resolution of the disease process was defined as attainment of a temperature difference of < 1° F between two feet on two different occasions. Patients with serum creatinine $\geq$ 3 mg/dL or with a history of BP exposure were excluded. For patients in group Z, if serum creatinine was $\geq$ 2 mg/dL, the dose of zoledronate was reduced to 2.5 mg. Patients in both the groups were offloaded using TCC. Forty patients completed the study

Table 1 Table of randomized controlled trials on bisphosphonates in acute Charcot foot

Ref.	BP	Duration (mo)	Jadad score	Subjects	Outcomes			
					Skin temp	Symptom score	BTM	Others
Jude *et al*[69]	Pamidronate	12	5	T: *n* = 21; 90 mg single IV infusion P: *n* =18; single IV infusion of NS	Significant reduction in both groups; more in T group at 4 wk (*P* < 0.01)	Significant improvement in T group from 3 – 12 mo (*P* < 0.01)	BSALP: Significantly greater reduction in T group till 12 wk (*P* < 0.03) uDPD crosslinks: Significant reduction in T group at 4 wk (*P* < 0.01)	
Pitocco *et al*[70]	Alendronate	6	1	T: *n* = 11; 70 mg once a week orally C: *n* = 9; no pharmacological treatment	Significant reduction in both groups	Signification reduction in T group at 6 mo (*P* < 0.05)	1CTP and uHP: Significant reduction in T Group (*P* < 0.05) BSALP: Greater reduction in T group (*P* = 0.06)	
Pakarinen *et al*[71]	Zoledronate	12	4	T: *n* = 20; 3 IV infusion of 4 mg at one monthly interval P: *n* = 19; placebo				Median immobilization time: Significantly greater in T group (*P* = 0.02)

BP: Bisphosphonate; T: Treatment group; P: Placebo group; C: Control group; IV: Intravenous; BTM: Bone turnover marker; BSALP: Bone specific alkaline phosphatase; 1CTP: Carboxyterminal telopeptide of type 1 collagen; uDPD: Urinary dehydroxypyridinoline; uHP: Urinary hydroxypronline.

(five patients withdrew), and 30 achieved complete resolution (16 patients in group Z and fourteen in group A). Five patients in each group achieved partial clinical resolution. The mean number of days required for complete healing process was around 122 d in both the groups.

Randomized controlled trials

All randomized controlled trials (RCTs) related to the use of BPs in acute CF are described in Table 1. In 2001, Jude *et al*[69] reported a 12 mo double-blind randomized placebo-controlled trial including 39 diabetic patients with acute CF. At baseline, 21 patients received single 90 mg infusion of pamidronate over 4 h, whereas 18 patients received normal saline (placebo). All patients received standard care of foot immobilization. For the first 3 mo, all patients were followed up at 2-weekly intervals and thereafter at 6, 9, and 12 mo. At each visit, patients were assessed for clinical symptoms, and skin temperature was measured with an infrared thermometer. BTMs like bone-specific ALP and urinary dehydroxypyridinoline were measured at each visit. Skin temperature reduced significantly in both the groups with pamidronate group showing a greater reduction at 4 wk. It dipped further during the study period with no intergroup difference on subsequent visits. Both groups demonstrated symptom score improvement at 3 mo. Following this, the score remained unchanged in the control group over the next 12 mo, whereas the

pamidronate group registered further improvement (*P* < 0.01). Bone-specific ALP showed a significant reduction in the pamidronate group when compared to placebo (*P* < 0.03) at 4 wk, and this was maintained for at least 12 wk. A similar trend was observed in urinary dehydroxypyridinoline at 4 wk (*P* < 0.01). Both the BTMs gradually increased towards baseline at 12 mo.

In an observer blinded RCT, Pitocco *et al*[70] studied the efficacy of alendronate in patients with acute CF. Eleven patients included in study group received alendronate 70 mg orally once a week while nine patients in control group received no pharmacological treatment. All patients were followed up for 6 mo and were offloaded using a TCC boot for the first 2 mo, which was followed by a pneumatic walker in the subsequent 4 mo. BTMs like serum 1CTP, serum bone ALP, and urinary hydroxyproline were measured at baseline and at 6 mo of follow up. All these markers showed a significant reduction in the alendronate-treated group when compared to control group (*P* < 0.05), except for bone ALP (*P* = 0.06). Dual-energy x-ray absorptiometry done at baseline and at 6 mo showed statistically significant improvement in bone mineral density of total foot (*P* < 0.05) and distal phalanxes (*P* < 0.01) in the alendronate group. Visual analogue scale score for pain improved significantly in the treatment group, with no improvement in the control group (*P* < 0.05). Skin temperature reduced significantly in both groups at 6 mo.

In 2011, Pakarinen *et al*[71] first studied the effect of zoledronate in 39 diabetic subjects with acute CF in a double-blind randomized placebo-controlled trial. Patients were randomly assigned into two groups receiving three IV infusions of either 4 mg zoledronate or a placebo at 1-mo intervals. Patients with previous BP exposure or severe renal insufficiency were excluded. All patients were initially treated with a non-weight bearing cast and were allowed partial weight bearing when the clinical signs of active CF process subsided. Complete weight bearing was allowed only when the temperature difference between the two feet was less than 1℃ for at least last 30 d with no evidence of edema or erythema. All patients were evaluated at baseline, at 2 to 4 wk intervals for the first 3 mo and then at 6, 9, and 12 mo. Finally, 35 patients who completed 12 mo follow-up were analyzed. The final endpoint of this study was median immobilization time, which was significantly longer in the zoledronate treated group as compared to the placebo group (27 wk *vs* 20 wk, *P* = 0.02). No information was given regarding BTMs or radiological findings at any point of time. During 12 mo follow-up, one patient relapsed in each group.

DISCUSSION

The main aims of treatment in acute CF are to relieve the patient of symptoms and to avoid complications, such as deformity and ulceration, thus preventing the progression to chronic CF. Immobilization and off-loading are the most important components of this treatment. Avoidance of repetitive microtrauma leads to the resolution of edema and swelling. Casting should be continued until the skin temperature difference between the two limbs becomes less than 2℃[16]. However, the basic pathogenesis in CF revolves around osteolysis, which leads to subsequent bone destruction, and immobilization does not address this directly. This creates space for the adjuvant therapy that can inhibit osteolysis and hence bone resorption. BPs, calcitonin, and denosumab are the anti-resorptive agents used to date in these patients. Among BPs, maximum evidence in the literature is available for pamidronate[72]. In a majority of case reports and series, pamidronate was shown to reduce the markers of activity of CF, like skin temperature, pain, edema, and BTMs. In the first RCT assessing the response of BP in acute CF, Jude *et al*[69] confirmed the beneficial effects of pamidronate in patients with acute CF. This RCT was of high methodological quality, as it was a double-blind, placebo controlled, multi-center study with proper mention about randomization process and statistical analysis. In a retrospective case-control study, Anderson *et al*[66] reported significant reduction in skin temperature and serum ALP in the pamidronate treated group. However, in a case series by Pakarinen *et al*[63], no difference was found for casting times when pamidronate was used along with conventional measures. Among other BPs,

alendronate in a RCT was shown to reduce pain and BTMs significantly in acute Charcot neuroarthropathy[70]. Additionally, zoledronate, the most potent third generation BP, was surprisingly shown to prolong immobilization times of patients with acute CF[71]. The limitations of this particular RCT were its underpowered nature (due its small sample size) and the discrepancy in the immobilization times. The latest randomized comparative study evaluating the effects of zoledronate and alendronate concluded that both medications had the same response in terms of clinical resolution time and scintigraphic changes. When cost was taken into account, however, alendronate was much less expensive than zoledronate[68].

None of these studies have ventured into the effect of BP on long-term outcome measures like avoidance of ulcerations, deformities, and amputation. The evidence from the available studies is limited because of the non-uniformity in the agent used and heterogeneity in outcome measures. Most studies, except one of Jude *et al*[69], have methodological flaws like open randomization, lack of blinding, and statistically small sample size. In fact, only Jude *et al*[69] reported the power analysis.

CLINICAL IMPLICATION

Oral alendronate and IV pamidronate have been efficacious in relieving symptoms and controlling disease activity in patients with acute CF. Oral BPs need to be taken on an empty stomach and with a full glass of water (at least 240 mL) to avoid getting it stuck in the esophagus. The patient should remain in erect posture for at least 30-60 min. Oral BPs have very poor bioavailability, with < 1% of the drug being absorbed from gastrointestinal tract[73]. BP should be taken in the fasting state with avoidance of any food for 30-60 min after taking to prevent its absorption from decreasing further. Retained gastric contents in patients with gastroparesis may also hamper absorption. Contraindications to oral BPs include an inability to follow this strict protocol, any active esophageal pathology like achalasia, varices, or stricture, or any malabsorption disorder like celiac disease, Crohn's disease, or post gastric bypass surgery[74]. For patients who cannot tolerate oral BPs, IV BPs can be an alternate option. IV BPs are known to cause acute phase reactions leading to flu-like illness in around 10%-30% of patients receiving their first infusion[74]. This can be taken care of by oral acetaminophen.

Vitamin D deficiency, which is common in the diabetic population, should be treated before giving BPs. In patients with renal insufficiency, caution should be exercised while using BPs, especially if glomerular filtration rate < 30-35 mL/min[74]. This is particularly true when given by rapid IV infusion, as it can aggravate or lead to renal dysfunction. Intranasal calcitonin can be an attractive option to treat acute CF in this group of patients. Moreover, BPs like zoledronate[75] and al-

endronate[76] have been linked with the occurrence of atrial fibrillation. HORIZON Pivotal Fracture Trial has shown a statistically significant increase in the incidence of serious atrial fibrillation in patients treated with zoledronate[75]. However, a large population-based study has refuted these findings[77].

As CN usually develops in diabetic patients with disease duration of more than 10 years, they are also expected to have gastroparesis, nephropathy, coronary artery disease, and various other complications. The above side-effects and contra-indications should be kept in mind while treating such patients with BPs.

CONCLUSION

The meteoric rise in the prevalence of DM has made it the most common cause of CN affecting foot and ankle. In a majority of the studies related to use of BPs in acute CF, pamidronate has been shown to reduce the markers of Charcot activity like skin temperature, pain, edema, and BTMs, but the quality of evidence is weak. Therefore, BPs can be considered as an adjuvant treatment option for acute CF.

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