

## Treatment Options for Charcot Neuroarthropathy

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### Abstract

Charcot neuroarthropathy is a complex and often under-detected problem in patients with diabetes complicated by peripheral neuropathy. Physicians must have a high index of suspicion to consider its diagnosis. Initial management involves offloading the foot, ideally with a total-contact cast. Intravenous bisphosphonates are used as medical therapy, and have been shown to reduce bone turnover markers and skin temperature. Surgery may be needed to address abnormal bone formation during the remodelling phase and produce a more stable foot. At all stages, a multidisciplinary approach is required for management.

### Keywords

Diabetes, neuropathy, diabetic foot, Charcot neuroarthropathy, bisphosphonates

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Charcot neuroarthropathy in the feet of patients with diabetes is not a common problem and is often under-diagnosed in clinical practice. Once it occurs, it can progress rapidly and result in severe foot deformity, increasing the risk of ulceration and amputation. Charcot foot is said to occur in approximately 0.2% of patients with diabetes.<sup>1</sup> Recognition and prompt treatment of the condition are critical to avoid complications, morbidity and potential mortality.<sup>2</sup>

Jean-Martin Charcot was the first to describe the changes of bone and joints in 1868, initially in patients with syphilis and neuropathy. However, it was not until 1936 that Jordan established an association between diabetic neuropathy and Charcot arthropathy.<sup>2</sup> Since then, there has been considerable progress in determining causative factors and aetiology of the Charcot foot and treatment options addressing the various factors involved. Despite this, a clear, definitive description of the processes involved remains elusive, although many theories exist.

### Clinical Course

Charcot neuroarthropathy occurs mostly in those patients whose diabetes is complicated by severe peripheral neuropathy. The initiating factor for development of a Charcot foot is minor trauma, which often goes unnoticed by the patient due to the lack of sensation in their feet. One study suggested that 73% of patients with Charcot foot did not recall a precipitating injury or event.<sup>1</sup> An early, acute phase then develops, in which the patient develops warmth, swelling and erythema of the foot, and indeed may also complain of pain despite the presence of advanced peripheral neuropathy. At this stage, misdiagnosis is common: patients may be diagnosed with cellulitis, septic arthritis, gout or minor injuries such as ankle sprains.<sup>3</sup> Foot radiographs at this stage often show no abnormalities, thus compounding the potential for misdiagnosis. However, if the condition

is recognised at this early stage, further development of significant abnormalities can be halted or reduced.

More chronic Charcot deformities will continue to develop if these early changes are not treated promptly. The increased blood flow to the foot together with the acute inflammatory reaction can lead to osteolysis and osteopaenia. Ligaments are also affected and can become lax. This then progresses to subluxation of the joints and fractures of the bones, changes that again may be unnoticed by the patient. The foot gradually becomes more disorganised and remodels, and the pressures placed on the foot when walking become increasingly abnormal, leading to ulceration or soft-tissue infections, which in turn can lead to osteomyelitis.

In the absence of developing infection, the Charcot joint can then enter a phase of coalescence, whereby the erythema decreases and bone destruction diminishes. The reconstruction stage follows this, when new bone forms and joint deformities fuse. This 'stabilisation' of the foot can result in significant permanent deformities, leading to risk of further ulceration in the future. The three-stage classification (development, coalescence, reconstruction) is known as the Eichenholz classification.<sup>4</sup>

The process can affect any of the joints within the foot or ankle, but most commonly affects those in the midfoot region. Midfoot Charcot neuroarthropathy causes a collapse of the arch of the foot, leading to a 'rocker-bottom' deformity. This subsequently causes abnormal pressure loading to the plantar surface of the foot.<sup>5</sup>

### Diagnosis

Successful diagnosis relies partly on the ability of the physician to suspect and recognise the potential for Charcot neuroarthropathy. It

should be considered in any patient with diabetes complicated by neuropathy presenting with a red, swollen, warm foot. The patient will have evidence of peripheral neuropathy on clinical examination, and will exhibit a difference in skin temperature between the two feet. A temperature difference of 4°C between the feet was considered significant in one study,<sup>6</sup> but differences can be higher.

Plain radiographs are the first-line investigation for Charcot neuroarthropathy, and Eichenholtz described radiological stages that corresponded to his clinical classification system.<sup>4</sup> Stage 1 (development stage) shows subchondral fragmentation and debris formation; stage 2 (coalescence) reveals the absorption of fine debris, fusing of larger fragments and sclerosis of bone ends; and stage 3 (reconstructive stage) involves the bone ends becoming more fully healed, with restoration of the joint architecture.

The major differential diagnosis for Charcot neuroarthropathy is osteomyelitis. Rogers and Bevilacqua proposed an algorithm to help distinguish the two conditions, stating that bone destruction on X-ray, in the absence of an open wound, was sufficient to diagnose Charcot neuroarthropathy.<sup>7</sup> In other cases, technetium bone scanning or magnetic resonance imaging (MRI) scans<sup>3</sup> should be used to differentiate osteomyelitis from Charcot foot, not forgetting that Charcot and osteomyelitis can be present simultaneously in the same foot.

## Early Treatment in the Acute Stage

As mentioned above, early treatment of the acute phase of Charcot neuroarthropathy is immensely important and results in vastly improved outcomes for the patient. Regular foot education for patients with peripheral neuropathy plays an important role in preventing injury and recognising symptoms at an early stage of development. Patients with Charcot neuroarthropathy should be referred to a specialist diabetic foot clinic for management, where a multidisciplinary team of nurses, podiatrists and doctors should be involved in their care.<sup>8</sup>

The mainstay of treatment in the early acute phase is offloading of the foot and reduction of weight-bearing, with the aim of arresting the process before the more chronic deformities have a chance to develop. Pain management is also important. Monitoring of disease activity can be achieved by clinical means (measures of skin temperature or erythema), serial radiographs or biochemical measures of bone activity.<sup>9</sup> These biochemical measures include markers of increased bone turnover, such as elevated alkaline phosphatase. Other markers of collagen breakdown products include urinary cross-linked N-telopeptides of type 1 collagen (NTX) or serum pyridonoline cross-linked carboxy-terminal telopeptide domain of type 1 collagen (1CTP). Elevation of these markers suggests increased bone turnover,<sup>9</sup> but they are not currently used in routine clinical practice. Although we use bone scanning to aid diagnosis, we do not currently use it for monitoring disease activity as it is expensive and not readily available.

## Physical Management

Offloading in the acute phase aims to eliminate the stresses to which the foot is subjected, and therefore to avoid the occurrence of microfractures and early joint deformities.<sup>10</sup> The gold standard device to achieve this is a total-contact cast (TCC), which is designed to be in contact with the whole plantar surface of the foot, thus eliminating areas of abnormal pressure distribution. The cast should be worn

continually and patients should be kept immobilised. Use of a TCC without weight-bearing can result in improvement in clinical markers within two weeks of application of the cast.<sup>11</sup> However, the cast is usually applied for 12–18 weeks.<sup>1</sup>

A TCC requires specialist expertise to fit correctly, and may not be available in all centres. Alternative devices include removable cast walkers, or an instant TCC (iTCC), which is a removable walker held in place by cohesive bandages. It has been proved that better results are obtained when these alternative devices are converted to iTCC rather than being used in their removable state.<sup>12</sup>

Once the acute phase has settled, physical management still plays an important role. The iTCC or removable walker can be used during the coalescent phase of Charcot neuroarthropathy. Specially designed shoes play a crucial role in long-term management of Charcot feet, as extra-depth or pressure-relieving orthoses can prevent further ulceration secondary to the resulting chronic foot changes. Other options include ankle foot orthosis (AFO) or Charcot restraint orthotic walker (CROW).<sup>10</sup>

## Medical Therapy

Medical therapy for Charcot neuroarthropathy is aimed at the increased bone turnover experienced during the acute phase.<sup>13</sup> Excessive bone turnover and increased osteoclastic activity have been described in several papers.<sup>14,15</sup> Selby et al. showed that patients with Charcot arthropathy have high levels of urine deoxypyridoline and bone-specific alkaline phosphatase, inferring high bone resorption and active bone formation.<sup>16</sup> Medical treatment was therefore postulated to be similar to other conditions with high turnover of bone, such as metastatic bone disease and Paget's disease of bone.

## Use of Bisphosphonates

Bisphosphonates were first trialled in 1994 by Selby and colleagues. They administered a course of pamidronate infusions over 10 weeks to patients with Charcot, and found improved symptoms, reduced foot temperatures and a 25% reduction in alkaline phosphatase levels.<sup>17</sup> This was followed by a larger, randomised, double-blind, placebo-controlled trial using 90mg pamidronate versus normal saline infusion as placebo. This was conducted by Jude et al. in four UK centres.<sup>11</sup> The treated group experienced a greater (but not significant) fall in temperature of the affected foot after two weeks, and improvement in reported symptoms. Measures of bone turnover were also reduced in the treatment group, suggesting a therapeutic benefit for bisphosphonates in treatment of Charcot neuroarthropathy. Further studies have supported these results. Anderson and colleagues used pamidronate infusions and showed a statistically significant reduction in foot temperatures and reduced alkaline phosphatase levels in the treated group.<sup>18</sup> Pitocco et al. used oral alendronate in a randomised controlled trial.<sup>19</sup> They found a significant reduction in foot temperature after six months in both treatment and placebo groups, but patients treated with alendronate had a significant difference in the reduction of 1CTP levels and improvement in bone mineral density from the placebo group. Further studies comparing different bisphosphonates and different dosing regimens could be beneficial.

## Use of Calcitonin

Calcitonin is similarly known to inhibit osteoclast function and reduce the number of osteoclasts in circulation. It is usually produced by the

thyroid medulla. It has a safer profile for use in renal failure compared with bisphosphonates. However, its major disadvantage is that it is more difficult to administer than bisphosphonates. Bem et al. carried out a trial of intranasal calcitonin as a treatment for acute Charcot arthropathy.<sup>20</sup> They found that the treatment group had a greater reduction in 1CTP levels (measure of bone turnover activity) compared with control subjects, but, again, no difference in reduction of skin temperature between the two groups.

### Other Medical Therapies

Further medical therapies for treatment of Charcot feet are under investigation. Current research is targeting the inflammatory pathways involved in the activation of osteoclasts and formation of a Charcot joint.<sup>13</sup> Various cytokines have been implicated in the inflammatory pathways and formation of osteoclasts, including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), IL-6 and parathyroid hormone. These could be potential targets for future immunomodulatory therapy. In addition, the receptor activator of nuclear factor-kappa B (NF- $\kappa$ B) ligand (RANKL) and osteoprotegerin molecules have been discovered; they are responsible for regulating osteoclast formation, and may be a further therapeutic target.<sup>21</sup> Finally, low-intensity ultrasound used in conjunction with other therapies may be beneficial.<sup>22</sup>

### Surgical Treatment

The traditional view of surgical treatment in Charcot neuroarthropathy was that it did not play a role in the acute active phase, but was important during the chronic phase. A study by Simon et al. raised the question as to whether surgery can be useful in the acute phase of Charcot neuroarthropathy.<sup>23</sup> They performed extensive debridement with arthrodesis of affected joints of 14 patients with active Charcot disease. The results were promising, with successful arthrodesis and no long-term complications reported.

Saltzman and colleagues suggested a need for surgery when they followed up 115 patients for a median 3.8 years after conservative treatment for Charcot foot.<sup>24</sup> They noted amputations in 2.7% and ulcer recurrence in 49.0%, some of which may have been prevented by earlier surgical intervention. The aims of surgical treatment are to produce a stable foot with minimal risk of ulceration and address the abnormal bone formed during the remodelling phase.

As Charcot neuroarthropathy patients often have significant co-morbidities and obesity, patients must have a full medical assessment including history and examination prior to any surgery. Patients should be aware of the prolonged recovery time following

these procedures, but also that, if successful, they could have improved walking ability and remain free from ulceration. It is important to assess the joint itself, together with the vascular supply to the limb, prior to surgery. Assessment should be made for any evidence of infection, and this should be eliminated prior to surgery where possible.<sup>25</sup> X-ray and computed tomography (CT) scans may be required to elucidate the anatomy of the joint prior to surgery. Surgical treatment can avoid potential amputations in the future if performed successfully.

Exostectomy is used in cases of stable Charcot foot whereby the bony remodelling has left a prominence of bone, causing abnormal pressure loading and ulcer formation. The procedure aims to simply remove the piece of protruding bone, reducing ulcer formation and making it easier to fit appropriate footwear. This should be performed via a lateral or medial incision to avoid the plantar surface of the foot. Rosenblum and colleagues performed 32 exostectomy procedures via lateral excisions, and noted a success rate of 89%.<sup>26</sup> Following surgery, a cast or splint should be used to immobilise the foot until healing occurs.

Arthrodesis is more commonly used for proximal joint disease or in cases where a Charcot deformity is very unstable and not amenable or correctable with treatment such as bracing or supports. The procedure aims to fix the relevant joints and provide a more stable foot. Major contraindications to the procedure include factors that may incur poor healing such as poor diabetic control or peripheral vascular disease.<sup>27</sup> The patient must again be aware that a prolonged recovery period following the procedure may be needed. Various devices can be utilised to ensure internal fixation of the joints to be fused.

Contracture of the Achilles tendon is commonly found in patients with Charcot deformities and, if found, lengthening of the tendon should be considered at the time of surgery.

### Conclusions

The management of patients with Charcot neuroarthropathy clearly involves a multidisciplinary team approach and co-ordinated management. It is a complex process that is under-recognised in clinical practice, leading to delays in diagnosis and appropriate management. Conservative management can be effective if the condition is recognised and treated quickly. However, if allowed to develop, severe deformities can occur and cause considerable morbidity and potential limb loss for the patient. Additional treatment options for this condition are under investigation, and will continue to develop as our understanding of the pathophysiology of the condition is further enhanced. ■

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