

# Intranasal Calcitonin in the Treatment of Acute Charcot Neuroosteoarthropathy

A randomized controlled trial

ROBERT BEM, MD<sup>1</sup>  
ALEXANDRA JIRKOVSKÁ, MD, PHD<sup>1</sup>  
VLADIMÍRA FEJFAROVÁ, MD<sup>1</sup>

JELENA SKIBOVÁ<sup>1</sup>  
EDWARD B. JUDE, MD, FRCP<sup>2</sup>

**C**harcot neuroosteoarthropathy (CNO) can lead to disruption of the bone architecture of the foot (1). Increased osteoclastic activity is believed to be responsible for the bone destruction in CNO (2). Previous studies showed COOH-terminal telopeptide region of type 1 collagen (1CTP) and bone-specific alkaline phosphatase (BALP) as useful markers of bone turnover in patients with CNO (3–5).

Presently, only bisphosphonates have been demonstrated to have some benefit in patients with CNO (6). However, bisphosphonates may have potential disadvantages in that they decrease bone remodeling and are contraindicated in patients with renal insufficiency (7).

Our previous study (8) showed positive effects of calcitonin on bone resorption in patients with acute CNO. In this study, we set out to assess the effect of calcitonin on bone metabolism and disease activity during a 6-month treatment with intranasal calcitonin in acute CNO.

## RESEARCH DESIGN AND METHODS

Thirty-two consecutive patients with acute CNO were entered into the study. Subjects were recruited from our diabetic foot clinic during a 17-month period and were followed up for 6 months. The study was approved by the local ethics committee, and all participants gave written informed consent.

Acute CNO was defined by clinical

signs: warm, swollen foot and skin temperatures  $\geq 2^{\circ}\text{C}$  at the site of maximum deformity of the affected foot compared with a similar site on the contralateral foot (infrared thermometer) and confirmed by plain X-ray and three-phase technetium bone scan (9). The presence of diabetic neuropathy was determined by measurement of vibration perception threshold  $>25$  V on the tip of the hallux, using a biothesiometer (10). Osteomyelitis was excluded by the absence of clinical and laboratory signs of acute inflammation. Two patients in each group ulcerated during the study period. The midfoot was the most commonly affected site ( $n = 26$ ) with no difference between groups.

Participants were randomized to receive salmon calcitonin nasal spray 200 IU daily with calcium supplementation (study group) or calcium supplementation only (control group) using a computer-generated randomization list. All patients also had standard treatment of the CNO, including off-loading by removable contact cast or cast walkers (11).

Disease activity was monitored by skin temperature measurement and markers of bone turnover: 1CTP (Orion Diagnostica, Espoo, Finland) and BALP (Tandem-R Ostase; Beckman Coulter, Fullerton, CA) were measured at each visit (monthly for the first 3 months and then at 6 months). Renal insufficiency was defined as an increased serum creatinine of  $>120$   $\mu\text{mol/l}$ , and five study pa-

tients and four control subjects had renal failures.

The sample size required for the study was 32 patients, which gave a power of 80% to detect a difference of 15% between the intervention and control groups with a two-sided  $\alpha$  of 0.05. Data were analyzed by means of Wilcoxon rank test and Mann-Whitney two-sample test, and  $P < 0.05$  was considered significant.

**RESULTS**— There was no difference in age ( $52.18 \pm 10.3$  and  $54.93 \pm 9.9$  years; study versus control groups, respectively), type of diabetes, or sex between the two groups (type 2 diabetes and male sex: 11 patients per group) and no difference in severity of neuropathy (vibration perception threshold  $42.9 \pm 10.1$  vs.  $40.1 \pm 8.9$  V). In addition, there were no differences in disease activity as assessed by skin temperature difference ( $3.5 \pm 0.9$  vs.  $3.6 \pm 0.8^{\circ}\text{C}$ ), 1CTP ( $9.82 \pm 2.17$  vs.  $9.73 \pm 2.02$   $\mu\text{g/l}$ ), and BALP ( $15.39 \pm 6.25$  vs.  $15.44 \pm 4.99$   $\mu\text{g/l}$ ) between groups at the beginning of the study.

The study group had significantly greater reduction in 1CTP in comparison with the control group during the first 3 months (1st month  $8.12 \pm 1.39$  vs.  $9.48 \pm 0.93$   $\mu\text{g/l}$ , 2nd month  $7.96 \pm 1.11$  vs.  $8.97 \pm 0.75$   $\mu\text{g/l}$ , and 3rd month  $7.63 \pm 0.87$  vs.  $8.74 \pm 0.74$   $\mu\text{g/l}$ ; all  $P < 0.01$ ); similarly, 1CTP reduction was seen in the subgroup of nine patients with renal insufficiency. Significant reduction of BALP was seen in the study group at 3 months in comparison with the control group ( $12.06 \pm 4.02$  vs.  $13.72 \pm 2.11$   $\mu\text{g/l}$ ;  $P < 0.05$ ); however, no difference in BALP was seen at 6 months between groups. Skin temperature of the affected foot significantly decreased in both groups; maximum reduction seen at 3 months ( $1.4 \pm 0.4$  and  $1.5 \pm 0.5^{\circ}\text{C}$  vs. baseline; study and control groups, respectively;  $P < 0.001$ ) with no significant differences between groups (Fig. 1).

**CONCLUSIONS**— We have shown that intranasal calcitonin treatment in pa-

From the <sup>1</sup>Diabetes Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; and the <sup>2</sup>Diabetes Centre, Tameside General Hospital, Ashton-Under-Lyne, Lancashire, U.K.

Address correspondence and reprint requests to Robert Bem, MD, Diabetes Centre, Institute for Clinical and Experimental Medicine, Videnska 1958/9, Prague 4, 14021, Czech Republic. E-mail: bemrob@yahoo.co.uk.

Received for publication 16 February 2006 and accepted 17 February 2006.

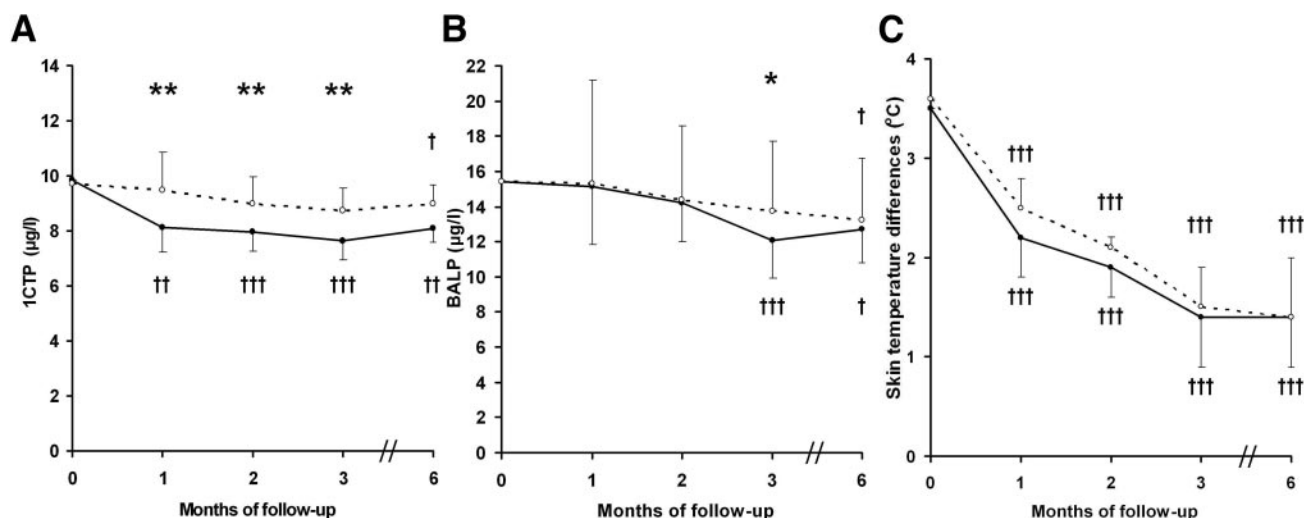
**Abbreviations:** 1CTP, COOH-terminal telopeptide region of type 1 collagen; BALP, bone-specific alkaline phosphatase; CNO, Charcot neuroosteoarthropathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0376. Clinical trial reg. no. ISRCTN91576704.

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.



**Figure 1**—Effect of calcitonin on 1CTP (A), BALP (B), and skin temperature differences (C) in the control (dashed line) and calcitonin-treated (solid line) groups. Data are means  $\pm$  SE. Study group vs. control group: \* $P < 0.05$ , \*\* $P < 0.01$ ; study group and control group vs. baseline: † $P < 0.05$ , †† $P < 0.01$ , ††† $P < 0.001$ .

tients with acute CNO significantly reduced bone turnover compared with standard therapy during the first 3 months of follow-up. In contrast to previous studies with bisphosphonates, our study included patients with renal insufficiency, who comprised 28% of the group.

The current standard treatment recommended for CNO includes off-loading and decreased weight bearing of the affected foot (12). Recent work has shown that bisphosphonates might be useful in the acute phase of CNO (3,13,14). However, one experimental study demonstrated that bone remodeling is strongly suppressed by high doses of bisphosphonates (15).

Calcitonin may have some advantageous effects in comparison with bisphosphonates. Bisphosphonates inhibit the action of osteoclasts, although not by impacting directly on the osteoprotegerin/receptor-activator nuclear factor  $\kappa$ B ligand system (16) in contrast to calcitonin, which impacts directly on this signaling pathway. Bisphosphonates can cause total inhibition of calcifying colony-forming units (17) contrary to the cessation of the osteoclast bone resorption by calcitonin, which was not accompanied by a decreased activity of osteoblasts (18). For these reasons, it might be logical to consider treating patients with calcitonin rather than bisphosphonates (16).

Reduction of bone resorption markers has been demonstrated in patients treated with bisphosphonates (3,13) as well as bone formation markers (3). In

our study, 1CTP and BALP significantly decreased in both groups in comparison with baseline values. In addition, a significantly greater reduction in the study group was seen. Calcitonin reduced 1CTP in comparison with baseline values throughout follow-up, whereas in the control group, a significant reduction in 1CTP was seen only at the end of the study. Similar to the Pamidronate Study (3), we also demonstrated skin temperature reduction in both groups with no differences between groups, probably due to the fact that all patients received off-loading measures (3). Although no study has previously been done in acute CNO, the effect of intranasal calcitonin on bone remodeling in postmenopausal osteoporosis is proven (19).

In conclusion, this study suggests that intranasal calcitonin treatment of acute CNO, including patients with renal insufficiency, could be an effective modality to prevent bone resorption and progression of this condition, although larger clinical trials are needed to assess the role of calcitonin in patients with acute CNO.

**Acknowledgments**— This study was supported by grant MZO 00023001.

#### References

- Sanders LJ, Frykberg RG: Diabetic neuropathic osteoarthropathy: Charcot foot. In *The High Risk Foot in Diabetes Mellitus*. Levin ME, O'Neal LW, Bowker JH, Eds. New York, Churchill Livingstone, 1991, p. 297–338
- Young MJ, Marshall A, Adams JE, Selby PL, Boulton AJM: Osteopenia, neurological dysfunction, and the development of Charcot neuroarthropathy. *Diabetes Care* 18:34–38, 1995
- Jude EB, Selby PL, Burgess J, Liljestone P, Mawer EB, Page SR, Donohoe M, Foster AVM, Edmonds ME, Boulton AJM: Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomised controlled trial. *Diabetologia* 44:2032–2037, 2001
- Gough A, Abbraha H, Li F, Purewal TS, Foster AVM, Watkins PJ, Moniz C, Edmonds ME: Measurement of markers of osteoclast and osteoblast activity in patients with acute and chronic diabetic Charcot neuroarthropathy. *Diabet Med* 14:527–531, 1997
- Jirkovska A, Kasalicky P, Boucek P, Hosova J, Skibova J: Calcaneal ultrasonometry in patients with Charcot osteoarthropathy and its relationship with densitometry in the lumbar spine and femoral neck and with markers of bone turnover. *Diabet Med* 18:495–500, 2001
- Jude EB, Boulton AJ: Medical treatment of Charcot's arthropathy. *J Am Podiatr Med Assoc* 92:381–383, 2002
- Stepan JJ, Alenfeld F, Boivin G, Feyen HM, Lakatos P: Mechanisms of action of antiresorptive therapies of postmenopausal osteoporosis. *Endocr Regul* 37:227–240, 2003
- Jirkovska A, Hosova J, Kasalicky P, Skibova J: Biochemical markers of bone turnover in patients with Charcot osteoarthropathy before and after treatment. In *Poster of the 3rd International Symposium of the Diabetic Foot*. Noordwijkerhout, The Netherlands, International Working Group on the Diabetic Foot, 1999, p. 87
- Cavanagh PR, Young MJ, Adams JE, Vick-

- ers KL, Boulton AJM: Radiographic abnormalities in the feet of patients with diabetic neuropathy. *Diabetes Care* 17: 201–209, 1994
10. Young MJ, Breddy JL, Veves A, Boulton AJM: The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: a prospective study. *Diabetes Care* 17:557–560, 1994
  11. Armstrong DG, Tood WF, Lavery LA, Harkless LB, Bushmann TR: The natural history of acute Charcot's arthropathy in a diabetic foot speciality clinic. *Diabet Med* 14:357–363, 1997
  12. Rajbhandari SM, Jenkins RC, Davies C, Tesfaye S: Charcot neuroarthropathy in diabetes mellitus. *Diabetologia* 45:1085–1096, 2002
  13. Pitocco D, Ruotolo V, Caputo S, Mancini L, Collina CM, Manto A, Caradonna P, Ghirlanda G: Six-month treatment with alendronate in acute Charcot neuroarthropathy: a randomized controlled trial (Brief Report). *Diabetes Care* 28:1214–1215, 2005
  14. Selby PL, Young MJ, Boulton AJ: Bisphosphonates: a new treatment for diabetic Charcot neuroarthropathy? *Diabet Med* 11:28–31, 1994
  15. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB: Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone* 28: 524–531, 2001
  16. Jeffcoate W: Vascular calcification and osteolysis in diabetic neuropathy: is RANK-L the missing link? *Diabetologia* 47:1488–1492, 2004
  17. Still K, Phipps RJ, Scutt A: Effects of risedronate, alendronate, and etidronate on the viability and activity of rat bone marrow stromal cells in vitro. *Calcif Tissue Int* 72:145–150, 2003
  18. Zikan V, Stepan J: Plasma type 1 collagen cross-linked C-telopeptide: a sensitive marker of acute effects of salmon calcitonin on bone resorption. *Clin Chim Acta* 316:63–69, 2002
  19. Cranney A, Tugwell P, Zytaruk N, Robinson V, Weaver B, Shea B, Wells G, Adachi J, Waldegger L, Guyatt G, the Osteoporosis Methodology Group, the Osteoporosis Research Advisory Group: Meta-analyses of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. *Endocr Rev* 23:540–551, 2002