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Levels of Endothelial Nitric Oxide Synthetase Isoform, and Calcitonin Gene Related Peptide in Charcot Neuroarthropathy

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Charcot neuroarthropathy (CN) is a disabling and devastating condition affecting patients with severe diabetic neuropathy which can lead to foot deformity, foot ulceration and lower extremity amputation. The incidence of CN is about 0.1 to 23% in diabetic neuropathy. The pathogenesis of CN is not clear, but one possible predisposing factor is increase in bone turnover. Nitric Oxide (NO) is a free radical gas which has been implicated as a secondary messenger molecule in many biological pathways, in particular to suppress the function of osteoclasts. NO arises from a reaction regulated by a family of isoenzymes which are endothelial nitric oxide synthetase (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS). eNOS modulates the proliferation and function of osteoclasts. Regulation of eNOS is often associated with the presence of the neuropeptide calcitonin gene related peptide (CGRP). CGRP is a product of sensory nerve fibers and its presence is reduced in diabetic neuropathy. In addition, it has been shown that ablation of CGRP results in osteopenia due to reduced osteoblastic bone formation. Therefore, there may be an association between the decrease in CGRP and potential eNOS activity in CN. To investigate this possibility, we studied bone samples from normal subjects (n=4), subjects with diabetic neuropathy (n=4), and subjects with diabetes and CN (n= 4). We investigated the differences of cellular components (osteoblasts and osteoclasts) in H&E stains, and used immunohistochemical techniques to immunolocalize CGRP and eNOS in bone samples.

H&E stains demonstrated increased numbers of osteoblasts and osteoclasts in bone samples from subjects with CN and diabetic neuropathy compared to those from normal subjects. In CN specimens, immunolocalization of CGRP and eNOS intensifies at the margin of trabecular bone, osteocytes, and osteoclasts cytoplasm compared to normal bone. No difference of CGRP and eNOS immunolocalization was noticeable between CN and DN specimens. Thus, CGRP and eNOS may regulate osteoblastic and osteoclastic activity in patients with diabetic neuropathy.