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DIABETIC OSTEOPATHY

A STUDY IN THE RAT

AKADEMISK AVHANDLING

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ABSTRACT - DIABETIC OSTEOPATHY. A STUDY IN THE RAT

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The present study on non-obese Goto-Kakizaki (GK) rats with type-2 diabetes and neuropathy was an attempt to describe and define pertinent features of diabetic osteopathy. Altogether, the study included 33 GK rats aged 12 and 20 months, and 36 age-matched Wistar rats as controls. All underwent test of glucose tolerance and nerve (sciatic) conduction velocity (NCV) showing that the diabetic rats had significantly higher blood glucose levels and lower NCV confirming the presence of diabetes and neuropathy.

Skeletal features Radiologic analysis of bone entailed X-ray, Dual Energy X-ray Absorptiometry (DEXA) and peripheral Quantitative Computed Tomography (pQCT). In diabetic rats, the length of humerus and height of vertebrae was reduced by 8%. The long bones exhibited endosteal erosion of the diaphyses up to 18% and periosteal expansion up to 8%. The vertebrae and metaphyses of long bones showed a decrease up to 24% in areal bone mineral density (BMD), whereas no decrease was seen in the diaphyses. Cross-sectional measurements by pQCT showed a decrease in volumetric BMD ranging from 33 to 62%, which exclusively pertained to trabecular bone (vertebrae, metaphyses), whereas volumetric BMD of the cortical bone of diaphyses was only marginally affected. The results indicate that juxta-articular bone in diabetes is substantially weaker, whereas diaphyseal cortical bone may be even stronger. Over all, the observations suggest that the diabetic skeleton is characterized by regional changes, which cannot be explained by systemic factors like calcium regulating hormones. Local bone turn-over is regulated by complex mechanisms involving cytokines, prostaglandins, growth factors and, also neuropeptides. Further analysis focused on the insulin-like growth factor (IGF) system and neuronal mediators in bone.

IGF system Immunoassays of IGF-I were done on serum, ankle samples and cortical preparations. In addition, the inhibitory IGF-I binding proteins, IGFBP-1 and -4 were analysed in serum. In diabetic rats, serum IGF-I was reduced by 18%, while IGFBP-1 and IGFBP-4 were increased by 89 and 20%, respectively. This complies with the lower BMD in the diabetic rats. In cortical bone, IGF-I was reduced by 38%, whereas no change was seen in ankles. The loss of IGF-I in cortical bone represents a novel finding. Given the cortical expansion observed in diabetic rats, the opposite was expected. Conceivably, loss of IGF-I results in endosteal erosion, which is compensated by periosteal expansion.

Neuropeptides The analyses focused on two sensory mediators, i.e. substance P (SP) and calcitonin gene-related peptide (CGRP), and one autonomic, i.e. neuropeptide Y (NPY). Immunohistochemistry was applied to ankles and tibial diaphyses, whereas radioimmunoassay (RIA) was used for separate preparations of periosteum, cortex and bone marrow from femur and tibia, whole ankles, dorsal root ganglia (DRG) and lumbar spinal cord. The morphological analysis showed SP, CGRP and NPY positive nerve fibers in bone and joints, which mostly were blood vessel related, although free terminals were also seen. In addition, NPY-positive hematopoietic cells were observed in the bone marrow. RIA revealed a significant decrease of CGRP, albeit not of SP, in DRG (-26%) and spinal cord (-29%) in the diabetic rats. As for bone, only NPY was significantly reduced, most evidently in bone marrow (-66%), but also in cortical bone (-36%) and ankles (-29%). Given the bone anabolic effects of CGRP and NPY, loss of these neuropeptides may prove, at least partly, to underlie the trabecular osteopenia and endocortical erosion observed in diabetic rats.

Conclusion The skeleton of diabetic rats with type-2 diabetes and neuropathy is characterized by regional changes of size, form, mineral content and density and concomitantly with regional abnormalities of the IGF-system and neuropeptides suggesting that also local factors beyond systemic play an important role in the development of diabetic osteopathy.

Key words: Diabetes mellitus type 2, Goto-Kakizaki rat, bone mineral density, insulin-like growth factor-I, insulin-like growth factor binding protein 1, insulin-like growth factor binding protein 4, peripheral neuropathy, substance P, calcitonin gene-related peptide, neuropeptide Y