

Diabetes mellitus type 2 and osteoporosis

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Osteoporosis and diabetes mellitus are two diseases with high prevalence which are associated with an increase in the risk of fragility fractures, and with a substantial impact on the morbidity and the mortality of the population in general.

Although various observational studies have investigated the association between the two, the mechanism by which diabetes favours the appearance of fractures has not been properly established.

Most of the epidemiological studies carried out in patients with type 2 diabetes have shown an increase in bone mineral density¹, in spite of which there is an increased risk of fracture of 1.5 for hip fracture, proximal humerus and distal radius². In terms of the risk of vertebral fracture, the results are less uniform, although most of the studies also show an increase in risk^{3,4}.

Hyperglycemia exerts both direct effects on bone cells, especially the osteoblasts, and indirect effects through the formation of products deriving from glycation.

In vitro, high levels of glycemia stimulate or inhibit osteoblast proliferation as a function of the phase of the cell cycle. The differentiation of these cells is especially suppressed, which is shown in the decrease in the production of osteocalcin, of the deposit of calcium and in bone mineralisation. The expression of the receptors for parathormone and vitamin D are also reduced. In addition, the hyperglycemia affects the functionality of the osteoblasts through the induction of an osmotic response mediated by its sensitivity to the acid medium induced by the lactate⁵.

The hyperglycemia also changes the formation of the collagen fibres which reduces the formation of

the extracellular protein matrix and the mineralisation. The advanced glycation end products (AGEs) are formed *in vivo* through the Maillard reaction, a reduction of glucose with proteins to form an unstable product which later stabilises, resulting in an irreversible non-enzymatic and posttranscriptional modification of the protein involved⁶.

The high levels of AGEs and their accumulation play an essential role in the development of the complications associated with diabetes⁷. High levels of AGEs have been found in various tissues and have been related to low turnover of tissue in tendons, skin, amyloid plaques and cartilage. Their accumulation in the bone reduces the activity of the osteoblasts by the bonding of the AGE products with specific receptors (RAGE), alters osteoclastogenesis and reduces mineralisation. The collagen in the extracellular matrix modified by the AGEs is more difficult to eliminate by the hydrolytic enzymes, which increases bone fragility. The presence of AGEs also interferes in the interaction between the bone cells and the extracellular matrix⁵. Therefore, excess glycation may affect the properties of the bone, and this effect is evident above all in the cortex due to the accumulation of AGEs such as pentosidine in the parts of the skeleton with less rotation⁸.

In addition, acute and chronic hyperglycemia has been shown to suppress the expression of the genes associated with the maturation of the osteoblasts in rats with diabetes⁵. As a counter to this, Miranda Diaz et al. in an article published in this number have demonstrated that the gene expression of RANKL, RANKL/OPG ratio and Runx2 are found to be altered in cultures of osteoblasts from diabetic patients with hip fracture, this being increased⁹. The authors postulate that these fin-

dings would mean a higher number of less differentiated osteoblasts with a higher expression of RANKL, which means that there would be a greater activation of osteoclastogenesis, a higher rate of remodelling and, therefore, a negative influence on bone resistance. However, histomorphometric studies in patients with diabetes have shown a low recruitment of osteoblasts along with a reduction in the rate of mineral apposition¹⁰.

In short, to avoid glycation by controlling of hyperglycemia and the consequent reduction in AGEs should be the most effective tool to delay and minimise bone-related complications in diabetic patients.

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