Osteoporosis and steroid antagonists of the Wnt way

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The association between an excess of glucocorticoids and osteoporosis was indicated more than 80 years ago by Harvey Cushing when describing the disease which takes his name. Subsequently, after the introduction of the glucocorticoids as anti-inflammatory drugs, it was confirmed that exogenous hypercortisolism was also detrimental to the skeleton, in such a way that steroidal osteoporosis is now considered to be the most common form of secondary osteoporosis in our ambit[1]. Osteopenia induced by corticoids affects predominantly trabecular bone and is most intense during the first months of treatment, when more than 10% of bone mass may be lost[2]. In addition to inducing the loss of bone, the glucocorticoids alter its quality, which would explain the notable increase in fractures (nearly 75%) during the first three months of treatment, even before bone mineral density falls.

The mechanisms which are involved in the reduction in the quantity and quality of bone tissue are various. The glucocorticoids act directly on the osteoblasts, inhibiting their replication, differentiation and functional activity, and favouring both their apoptosis and that of the osteocytes[3,4]. They also act on the osteoclasts, reducing their proliferation but prolonging their survival[3,5]. On the other hand, the glucocorticoids exert an indirect effect on the generation of osteoblast cells by suppressing the expression of bone morphogenetic proteins (BMP), and of the Runx2 transcription factor, which is required to induce osteoblast differentiation from the mesenchymal mother cells[6]. In addition, these drugs increase the expression of PPARγ, which favours the differentiation mother cells into adipocytes and slows their differentiation into osteoblasts, contributing to an increase in fat in the bone marrow at the expense of the osteoblasts and of trabecular bone[7].

Finally, the corticoids may also intervene in the Wnt (wingless) pathway, which acts to modulate the differentiation and activity of bone cells. This complex signalling pathway is made up of a number of components, including ligands, membrane receptors, intracellular and antagonist effectors[8]. The best known mechanisms for transmission of the signal of the Wnt ligands are those included in what is called the canonical pathway, in which β-catenin plays a central role, although there are other alternative or non-canonical pathways which use different mediators[9]. The Wnt ligands are glucoproteins capable of bonding with their receptor and initiating the activity of the pathway. The membrane receptors are made up of frizzled proteins and proteins related to the receptor of low density lipoproteins type 5 and 6 (LRP5 and LRP6). Finally, various types of molecules have been described with an inhibitory action on the Wnt pathway. In some cases these are molecules which act as decoys which bond with to the Wnt ligands and thus compete with its bonding to the receptor. This is the case for some soluble proteins of the frizzled type which are secreted into the extracellular environment. Another inhibitor molecule is sclerostin, a glucoprotein of 190 amino-acids coded by the SOST gene which is expressed in the osteocytes and which bonds to LRP5/6, impeding the formation of the LRP 5/6-frizzled-Wnt complex. The sclerostin is released into the blood circulation, making it possible to determine its blood concentration[10]. There is a strong correlation between the content of sclerostin in the bone and its level in the blood, which would indicate that the production of this protein occurs in the bone and that its measurement in the blood may reflect its activity in the tissue[11].

Other molecules capable of antagonising the Wnt signals by bonding themselves to the LRP 5/6 and Kremen co-receptors are those of the dickkopf family. There are at least four members of this family of which the type 1 (Dkk-1) is especially significant in the bone[9,12,13]. Similarly to sclerostin, Dkk-1 may also be determined in the blood, with a higher concentration of this antagonist having been described in postmenopausal women or those with low bone mass. It has also been suggested that the reduction in the effect of teriparatide may be related to an increase in the concentrations of this antagonist[14].

In this edition of the Review of Osteoporosis and Mineral Metabolism Grifé et al.[15] analysed the values of blood sclerostin and Dkk-1 in patients who has started treatment with glucocorticoids, confirming that, contrary to what occurs in experimental studies, steroid treatment is associated with a reduction in Dkk-1, while no changes are observed in concentrations of sclerostin. As the authors note, there are various reasons which may justify these findings. Sex, age, renal function, estrogenic status, the existence of associated diseases or the quantity of bone mass are determining factors in levels of sclerostin and probably also of Dkk-1[14,16,17]. On the other hand, there is also the possibility that the blood values of both antagonists do not adequately reflect their expression in tissue. Moreover, contrary to what might be expected *a priori*, there was no relationship between the blood concentrations of the antagonists of the Wnt pathway and those of the markers for bone remodelling. However, it should be noted that the data published to date have been contradictory, with in some cases an inverse relationship between levels of sclerostin and some markers for formation having been described[17], while in other studies this relationship has not been able to be confirmed[16,18,19]. In any case, the results of this excellent work invite further studies which analyse the effect of glucocorticoids on the Wnt pathway antagonists, as well as their relationship with bone mass and markers for remodelling, which would without doubt help to clarify the role the Wnt pathway antagonists play in the development of steroidal osteoporosis.

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