PROSPECTIVE STUDY OF BONE LOSS AFTER SPINAL CORD INJURY. RISK FACTORS AND ROLE OF OSTEOCYTE MARKERS

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1. Summary of the project

The main objective of this project was to analyse the incidence of osteoporosis and fractures in patients with spinal cord injury (SCI) and the associated complications and to determine the physiopathology of this process in order to prevent and treat this clinical complication. With regard to the physiopathology of SCI, we analysed the markers of osteocytic function, sclerostin and Dkk-1 in patients with recent SCI and evaluated their relationship with bone remodelling markers, biochemical parameters of bone metabolism and the evolution of bone mineral density (BMD) in these patients. In addition, we identified the factors related to bone mass loss and the development of osteoporosis and fractures in these patients as well as possible treatment for the prevention of this pathology. A prospective 3-year study was carried out including 42 patients with recent traumatic SCI (<6 months). The characteristics of SCI were analysed as well as the evolution of BMD in the different skeletal areas, markers of bone remodelling and the parameters of mineral metabolism. We also studied the markers of osteocyte function at baseline and at 6, 12 and 18 months after SCI. The results were compared with a control group of individuals of the same age and gender.

2. Results

There is a marked increase in bone remodelling following SCI. This is shown by an increase in bone remodelling markers during the first year after SCI and a marked loss of bone mass below the level of the SCI (-20% in the proximal femur) (Figure 1) which is associated with an increase in serum Dkk-1 levels. In addition, the development of osteoporosis in this population is very frequent (greater than 50% develop osteoporosis within the first year of follow-up of SCI) and is especially relevant considering this is a young previously healthy population with a mean age of 35 years. Taking all of this into account, the persistently elevated Dkk-1 levels in patients with SCI and their relationship with the magnitude of bone mass lost suggest that this marker may play a role in this process and may be a potential therapeutic target in this clinical setting.

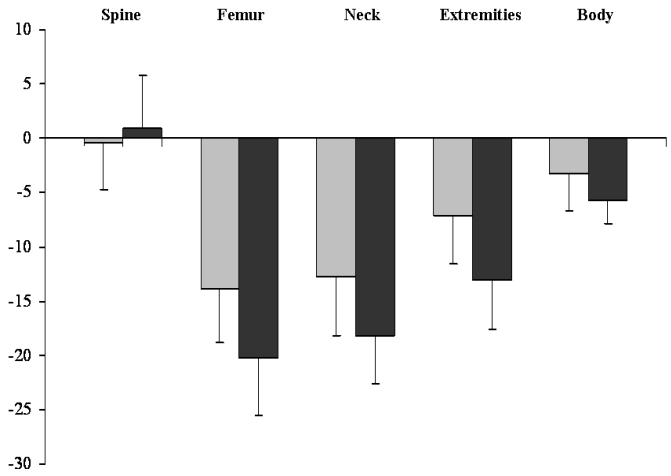

Figure 1. BMD change (%) in lumbar spine, femur (total and neck), lower extremities and total body at 6 months (grey bars) and 12 months (black bars) after SCI

The BMD values at the lumbar spine and proximal femur in patients with recent SCI are the main predictive factors for the development of osteoporosis during the first year after SCI. The results of the present study clearly indicate the need to assess and treat these patients early after SCI.

The incidence of fractures after SCI is high (25% of the patients with SCI ASIA A develop fractures within the first 10 years after SCI). The severity of SCI (ASIA A) and the length of SCI evolution (>6 years) are the main determining factors for the development of fractures in these patients. It is of note that fractures are frequently associated with clinical complications. However, the use of antiosteoporotic treatment in these patients is scarce.

Antiresorptive treatment with denosumab (anti-RANKL antibodies) increases BMD in the lumbar spine and proximal femur and reduces the values of bone remodelling markers in patients with osteoporosis associated with SCI. Thus, denosumab may be a good therapeutic option in patients with osteoporosis associated with SCI.

3. Relevance and possible implications

This prospective study with follow-up of patients with complete recent motor SCI has established the possible role of Dkk-1, an antagonist of the Wnt pathway, in the loss of

bone mass associated with SCI and its identification as a potential therapeutic target in this clinical setting. Moreover, this study has provided evidence that after SCI these patients present a marked loss of bone mass of around 20% at the level of the proximal femur at 12 months of follow-up, and this bone mass loss leads to the development of osteoporosis within the first year after SCI in 59% of these patients. In addition, the risk factors for developing osteoporosis during the first year after SCI as well as those for developing skeletal fractures were identified, observing a high incidence of fractures and associated clinical complications in these patients in our setting. Finally, for the first time, analysis of antiosteoporotic treatment, specifically with denosumab, initiated in patients who have developed osteoporosis after SCI has led to the identification of an effective therapy for the control of osteoporosis associated with SCI.

The results of this study have had a significant repercussion on the therapeutic approach to these patients since the results have been presented in several national and international congresses as well as different communication media and have been published in journals of scientific impact. In addition, our results have led to earlier identification and treatment of patients presenting a risk of developing osteoporosis after a spinal injury as well as those developing complications related to this process. Moreover, our findings have allowed the creation of a specialized care program specifically for these patients and suggest the need to develop clinical practice guidelines related to this clinical complication.

4. Literature generated

Publications

1. Incidence of skeletal fractures after spinal cord injury. A ten-year follow-up study. Gifre L, Vidal J, Portell E, Puig J, Monegal A, Guañabens N, Peris P. Clin Rehabil. 2014 Apr;28(4):361-9. doi: 10.1177/0269215513501905.

2. Effect of recent spinal cord injury on Wnt signaling antagonists (sclerostin and Dkk-1) and their relationship with bone loss. A 12-month prospective study. Gifre L, Vidal J, Carrasco J, Filella X, Ruiz-Gaspà S, Muxi A, Portell E, Monegal A, Guañabens N, Peris P. J Bone Miner Res. 2015 Jun;30(6):1014-21.

3. Risk factors for the development of osteoporosis after spinal cord injury. A 12-month follow-up study. L. Gifre, J. Vidal, J. L. Carrasco, A. Muxi, E. Portell, A. Monegal, N. Guañabens, P. Peris. Osteoporos Int 2015 Sep;26(9):2273-80.
4. Efecto de la lesión medular motora completa reciente en el remodelado óseo y en la evolución de la masa ósea. Gifre L, Vidal J, Ruiz-Gaspà S, Portell E, Monegal A, Muxi A, Guañabens N, Peris P. Rev Osteoporos Metab Miner 2014 6;4:97-102.
5. Denosumab increases sublesional bone mass in osteoporotic patients with recent spinal cord injury. L Gifre, J Vidal, JL Carrasco, A Muxi, E Portell, A Monegal, N Guañabens, P Peris. Osteoporos Int 2016 Jan; 27(1) 405-10.

Doctoral Thesis

Title: "Fisiopatología de la pérdida de masa ósea en los pacientes con lesión medular. Papel de los antagonistas de la vía Wnt (esclerosita y Dkk-1) y factores de riesgo relacionados con el desarrollo de osteoporosis y fracturas en estos pacientes"
Doctor: Laia Gifre Sala
Date: 20 November 2015.