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# Osteoporosis and osteoarthritis: two mutually exclusive diseases or two related entities?

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## Summary
The possible association between osteoporosis and osteoarthritis represents an ongoing matter of debate. It was considered, for decades, that both diseases were mutually exclusive due to the anthropometric characteristics and the difference in bone mass that patients with osteoporosis and osteoarthritis often present. However, in recent years, it was pointed out that both processes can coexist, and even that they may have a direct relationship. In this paper we review some aspects of the association between both diseases from a temporal perspective.

**Key words:** *musculoskeletal diseases, osteoarthritis, osteoporosis.*

## Introduction

Osteoporosis and arthrosis are the two most prevalent bone diseases, having considerable morbidity and being responsible for very high healthcare costs. Furthermore, the progressive aging of the population has resulted in a notable increase in their prevalence in the general population[1].

The possible relationship between arthrosis and osteoporosis has been the object of intense debate in the last four decades. In 1972, Foss and Byers[2] indicated that patients with hip fracture rarely had coxarthrosis. Subsequently, numerous studies have been published, often with contradictory results, as well as editorials and bibliographical reviews which have tried to give a clarifying perspective according to the evidence available at that the time. However, the different studies differ substantially in many methodological aspects, which makes their comparison, as well as the development of a synthesis of their results, difficult. In fact, at present the question posed does not appear to have singe answer.

For all these reasons, we are going to approach this problem from a temporal perspective, analysing the studies carried out in three consecutive periods. First, we consider the period between 1972 and 1996. Second, the period from 1996 to 2006; and finally, from 2006 to the present.

## Period 1972-1996

In a review published in 1996[3] 36 works carried out between 1972 and 1996 were analysed. These studies were mostly of a transverse design, and gave rise to two observations. One of these was the general clinical impression that no signs of arthrosis were found in the femoral necks extracted during surgery for hip fracture, and furthermore, that this type of fracture was infrequent in patients with coxarthrosis. The second observation was in the phenotype differences which are usually seen in patients with arthrosis or osteoporosis. So, while those patients with arthrosis tended to have an endomorphic biotype, those with osteoporosis usually have an ectomorphic biotype.

In terms of the primary objectives which were addressed in this period, most of the studies were aimed at examining the affect of arthrosis on bone mineral density (BMD). However, there was no uniform criterion for the evaluation of the characteristics of both osteoporosis and arthrosis. For example, on occasion, arthrosis was evaluated through a histological study of the femoral head obtained during surgery for hip fracture. At other times, it was evaluated by means of radiological imaging, essentially using the Kellgren-Lawrence scale, although occasionally other scales were also used, such as the Empire Rheumatism Council Criteria[4]. Finally, in some studies arthrosis was evaluated by the patients themselves using a structured survey ("self-reported osteoarthritis")[5]. In terms of osteoporosis, the measurements of bone mineral density are carried out with different procedures: radiological evaluation of the trabeculae of the proximal femur according to the Singh criteria[4], simple photonic absorptiometry[6], dual photonic absorptiometry[7], quantitative CAT[8] and histomorphometry[9].

The great majority of the studies, as we indicated earlier, were of a transverse design and, especially the older ones, do not include a statistical analysis which permits adjustment for possible confusion factors. In any case, in the majority of the works a significant increase in bone mass was seen in patients with arthrosis, which reached 4-10% in the spine and a little less (3-5%) in the apendicular skeleton. On the other hand, in those isolated cases in which both processes (coxarthrosis and hip fracture) coexisted, the age at which the fractures appeared was higher than that observed in the general population, which supported the idea that arthrosis may exert a protective effect against hip fracture[10]. Lastly, some studies put special emphasis on anthropometric and clinical differences which are observed in the two populations. The osteoporotic patient is usually thin, has a low body mass index and has a greater propensity to fractures, while the arthrosic patient could be, rather, a patient who is overweight, with an increased BMD and muscular strength, and a lower number of fractures[11]. Therefore, according to these first results, the existence of an inverse relationship between osteoporosis and arthrosis seems to have been confirmed. In fact, during this period it was suggested that the latter disease, or a factor related to it, could exert a protective effect against osteoporosis in general, as well as against hip fracture in particular.

## Period 1996-2006

Three facts characterise this second period: an advance in laboratory techniques, the establishment of dual energy X-ray densitometry (DXA) as the gold standard for the evaluation of bone, and the carrying out of studies on the arthrosis/osteoporosis relationship with designs which produced more substantial scientific evidence.

Intuitively, the relationship between arthrosis and osteoporosis was shown to be much more complex than had been supposed until then, and new lines of investigation, such as for example, the study of genes involved in both diseases, or the possible beneficial role of antiresorptive drugs on arthrosis. On the other hand, in various studies the existence of an unexpected association was observed between arthrosis of the hands and osteoporosis, as well as between spondyloarthrosis with vertebral fracture. Finally. in the light of new histochemical and imaging techniques (especially DXA), the results of the initial studies on load-bearing joints (hip and knee) have been reconsidered, which has resulted in the widespread opinion that arthrosis and osteoporosis were mutually exclusive diseases.

### *Bone mass and arthrosis*

In the Rotterdam cohort it was observed that, in spite of the fact that those patients with coxarthrosis had higher bone mineral density in the hip than people without arthrosis, the subsequent loss of bone mass, specifically in the two years follo-

wing the fracture, was greater in the arthrosic patients[12]. Furthermore, the loss of bone bore no relation to age, nor to the degree of incapacity of these patients.

On the other hand, Arden et al.[13] also observed that those patients with arthrosis in the hip had a higher BMD than the controls without arthrosis. However, after seven years of follow up the incidence of vertebral and non-vertebral fractures was similar on both groups.

***Markers for bone turnover***

In general terms, most of the studies carried out during these years showed that patients with arthrosis had increases in markers for resorption. Thus, Naitou et al.[14] confirmed that women with gonarthrosis and with generalised arthrosis had a urinary secretion of pyridinoline and deoxypyridinoline higher than in that in healthy women. Similarly, in another longitudinal study[15] it was demonstrated that postmenopausal women with gonarthrosis showed an increase in the urinary secretion of amino-terminal (NTX) and carboxy-terminal (CTX) telopeptides of collagen type 1, which were the same as those observed in women of the same age with osteoporosis. In terms of markers for formation, there is only one work published in this period[16], in which it was observed that the values for blood osteocalcin were lower in postmenopausal women diagnosed with arthrosis of the hands or knees than in healthy women of the same age.

***Antiresorptive drugs and subchondral bone***

In spite of arthrosis having been considered classically as a disease of cartilage, it is also possible that the subchondral bone plays some role in the initiation and progression of this disease[17]. On the one hand, the rigidity of subchondral bone appears to favour lesion of the joint cartilage, and on the other, once started, the damage to the cartilage would contribute to the progression of the arthrosis. However, at the end of the Nineties it was confirmed that the subchondral bone of the arthrosic joints had lower mineral content. This phenomenon was associated with an increase in bone turnover[15,18], which led to the suggestion that antiresorptive drugs may be of use in the treatment of arthrosis[19], although this suggestion was not shared by all authors[20]. In any case, in spite of the fact that in some studies favourable results were reported in patients treated with risedronate[21], alendronate or estrogens[22], these results were not able to be confirmed in other studies[23]. In fact, a review published in 2006 on therapeutic strategies for arthrosis[24] it was indicated that more studies would be necessary, perhaps in patients in whom the disease was less advanced, before considering the use of bisphosphonates in the treatment of arthrosis.

***Peripheral arthrosis and osteoporosis***

We have already said that arthrosis of some load-bearing joints such as the hip or knee is associated with a higher bone mass. In the case of arthrosis of the hands, less information was available, although the few results available suggested a similar association[25].

However, in this second period (1996-2006), some works were published which spoke against this possibility. Thus, in a transverse study it was observed that women with arthrosis in the hands had a lower bone mass in the hip than healthy women[26]. In the same vein, authors observed that erosive arthrosis in the hands was associated with lower T and Z-score indices in the lumbar spine than in controls[27]. Lastly, Haara et al.[28] confirmed that the loss of bone mass over 20 years, evaluated by means of quantitative ultrasound in the calcaneum, was more pronounced in those patients with arthrosis of the interphalangial joints.

***Spondyloarthrosis and vertebral fracture***

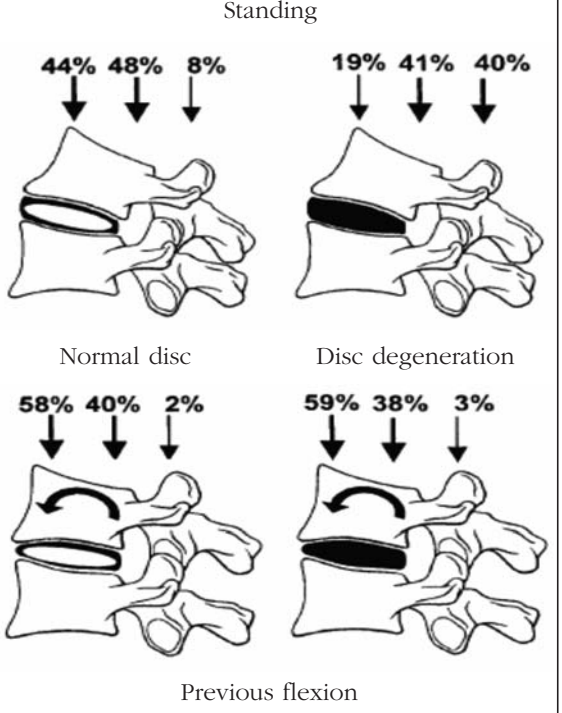
The trabecular bone in the vertebral bodies experiences a series of changes in its architecture (trabecular thinning, loss of interconnections, etc.) which are related to the loss of bone mass which occurs with age, especially in patients with osteoporosis. On the other hand, the vertebral bodies of patients with arthrosis may show other additional changes. For example, the posterior half of the vertebral bodies usually has a higher trabecular density than the anterior[29], which facilitates the appearance of vertebral fractures in those patients with spondyloarthrosis. In turn, these changes may have a relationship with the degeneration of the intervertebral disc. It is well known that the intervertebral discs and the vertebrae interact biologically and mechanically.

In fact, the relationship between the degeneration of the discs and the vertebral bone has been shown in histological and mechanical studies on vertebral segments from cadavers[30-32]. For some authors, the degeneration of the disc would reduce the height of the fibrous ring attracting the neural arches, in such a way that the pressure on the posterior arch would be displaced, improving the resistance to compression of the spinal column. However, the reduction in the mechanical stimulus on the anterior axis of the spinal column would entail in turn a reduction in trabecular volume and an increase in intratrabecular space in the anterior third of the, occasioning a significant reduction in its strength in comparison with the posterior third.

In normal conditions, in a flexing movement anterior to the vertebral column more than 50% of the compressive force is transferred to the anterior half of the vertebral body. In the presence of serious degeneration of the disc, anterior flexing increases the compressive force applied to the anterior zone of the vertebra by up to 300% (Figure 1). To this increased load may be added a reduction in bone mass and the poorer trabecular structure in the anterior third of the vertebra, which could increase the risk of fracture[31].

This sequence of events may explain both the regional variations in BMD of the trabecular bone of the vertebra, as well as the characteristic wedge deformity of the vertebral body in osteoporosis.

Figure 1. Distribution of pressure load in relation to the position of the spinal column and to the degree of degeneration of the intervertebral disc




Pollintine P, et al. Intervertebral disc degeneration can lead to "stress-shielding" of the anterior vertebral body -A cause of osteoporotic vertebral fracture? Spine. 2004;29:774-82.

In line with these findings, Arden et al.[33], in a case and control study, confirmed that the prevalence of vertebral fractures was greater in those patients with thoracic spondyloarthrosis. Subsequently, Sornay-Rendu et al.[34], in a longitudinal study carried out in 634 postmenopausal women from the OFELY cohort, observed that a reduction in intervertebral space is associated with an increased risk of vertebral fracture. The risk was even higher where arthrosis of the thoracic spine was concerned, and was independent of other factors such as age, previous fracture or BMD.

***Arthrosis in load-bearing joints (hip, knee) and osteoporosis***

In 2003 Glowacki et al.[35] analysed 68 postmenopausal women with advanced coxarthrosis and confirmed that a quarter of them complied with densitometric criteria for osteoporosis. In another study in which 119 patients with advanced arthrosis of the hip or knee participated (83 postmenopausal women and 35 men), it was observed that there was a prevalence of densitometric osteoporosis of around 30% in the women and 20% in the men[36]. Furthermore, over half the women and a third of the men had low bone mass. Therefore, for these authors, their results also contradicted the hypothesis that arthrosis and osteoporosis are two mutually exclusive diseases.

***Genetic studies***

Taking into account the polygenic hereditary character of both osteoporosis and of arthrosis, the possibility was raised that the two diseases shared some genetic determinants. For example, it has been indicated that certain polymorphisms in the gene for the receptor for vitamin D are associated with a greater degeneration of the intervertebral disc[37], and to an increase in the incidence of arthrosis of the knee, independently of the BMD[38,39]. There has also been an association reported of arthrosis with some allelic variants of the growth factor gene related to insulin type 1 (IGF-1)[40]. Other studies have centred on the possible participation of the Wnt pathway, which, as is known, modulates the differentiation of the pluripotent precursors, allowing their differentiation towards the formation of osteoblasts or to chondrocytes and adipocytes. In any case, the detailed analysis of these aspects exceeds the objectives of this review, so we will not detain ourselves further with it.

## Period 2006-2012

Among the most significant aspects of this period, what should first be noted is that a classical line of investigation, the relationship between arthrosis and osteoporosis in the hip, is deepened using the techniques currently available. Similarly to what had occurred previously with the antiresorptives, in this period a series of studies were carried out which analysed the possible beneficial role of strontium ranelate on arthrosis. On the other hand, studies appeared using animal models, in which both diseases were experimentally induced independently, which avoided interference from other confusion factors.

***Arthrosis of the hip and osteoporosis***

In a study carried out in 2007, Mäkinen et al.[41] investigated the presence of osteoporosis in 61 women with serious coxarthrosis, confirming that nearly a third of them had osteoporosis, while 45% had low bone mass. As might be expected, the osteoporotic women were older and weighed less than those who were not osteoporotic. In addition, they had an increase in markers for formation (PINP and osteocalcin) and resorption (NTx) which were inversely related to bone mass. Therefore, the authors suggested that arthrosis would not be capable of protecting women from suffering osteoporosis. However, in comparing the BMD in both hips in each patient, it was observed that the BMD in the femoral neck of the arthrosic hip was greater than that on the contralateral side, which may explain the lower prevalence of hip fracture which had been reported in patients with coxarthrosis[10].

On the other hand, in a study of cases (562 patients with hip fracture) and controls (803 subjects without that fracture) it was observed that patients with hip fracture had a lower risk of suf-

fering coxarthrosis, which would support the possibility that there might exist an inverse relation between the two processes[42]. However, in this study some confusion variables were not taken into account, such as the body mass index, physical activity, estrogen treatment or the use of bisphosphonate.

In an ultrastructural study carried out using electronic microscopy in 15 postmenopausal women (seven with coxarthrosis and eight with osteoporosis) who were subject to a hip arthroplasty, it was observed that the samples from the patients with arthrosis showed a higher level of new bone formation, the trabecular structure and the collagen fibres remaining intact[43]. On the other hand, in the women with osteoporosis, a marked trabecular reduction and thinning was observed.

Similarly, Marinović et al.[44], after analysing the femoral necks of 24 patients with advanced arthrosis and of 74 patients with hip fracture, observed that the patients with fracture had a wide variation in values of the different histomorphometric parameters related to trabecular bone (bone volume, trabecular separation, trabecular thickness, number of trabeculae), although in most of the cases they would differ from those observed in patients with coxarthrosis.

On the other hand, De Pedro et al.[45] arrived at opposite conclusions. These authors analysed 72 femoral heads obtained after arthroplasty in 56 patients with coxarthrosis and 26 patients who had suffered a hip fracture. The histological study demonstrated the changes which might be expected in both diseases: degenerative changes in the cartilage, cystic cavities and preservation of the thickness of the trabecular tissue in patients with arthrosis, as opposed to less trabecular tissue, thinner trabeculae and less quantity of osteoid tissue in the subjects with hip fracture. However, the histomorphic analysis revealed that more than 40% of those patients with arthrosis had a reduction in trabecular volume, which would support the idea of a coexistence between osteoporosis and arthrosis.

Finally, in recent times, Castaño-Betancourt et al.[46], in a study carried out in patients with atrophic arthrosis characterised by the existence of cartilage degradation without the formation of osteophytes, confirmed that patients with this type of arthrosis had lower BMD and a higher risk of fracture than patients with the usual forms of arthrosis, and than the healthy controls.

***Strontium ranelate and arthrosis***

Strontium ranelate is a drug used in the treatment of postmenopausal osteoporosis which has shown its efficacy in the reduction of vertebral and non-vertebral fractures[47,48]. Furthermore, in a post-hoc study carried out using grouped data from these studies[49], it was observed that treatment with strontium ranelate over three years would result in a reduction in the radiological progression of arthrosis in the spinal column in women with osteoporosis and spondyloarthrosis.

This effect was observed both in women with a previous vertebral fracture as well as in those with no fractures. Similarly, a recent clinical trial[50], has indicated that treatment with 1 or 2 grams daily of strontium ranelate over 3 years reduces the radiological progression of arthrosis in the knee, evaluated by the height of the internal femorotibial compartment. In addition, with a dose of 2 grams daily a greater improvement in symptoms was observed.

***Studies in animal models***

In 2007, Calvo et al.[51] published the results of an experimental study which tried to analyse the effect of osteoporosis and arthrosis in experimental animals. Arthrosis was induced in the knees of female rabbits by means of a section of the anterior cruciate ligament and partial meniscectomy, while the osteoporosis was provoked through bilateral oophorectomy and the administration of glucocorticoids. These authors observed that the osteoporosis increased the seriousness of the changes in the cartilage of the knee. Furthermore, the cartilage lesions were negatively correlated with the lumbar BMD, and with the subchondral bone, although in the latter, without being statistically significant. As a result, they suggest that, at least in this animal model, there would be a direct association between the two entities, although it is not known if the acceleration of the arthrosis induced by the osteoporosis is the result of an estrogen insufficiency, an alteration in the biomechanics of the subchondral bone, or of both at the same time.

For their part, Bellido et al.[52], using a similar model, arrived at the conclusion that the increase in resorption which is observed in the subchondral bone of the animals with osteoporosis would alter its quality, which would aggravate the damage in the cartilage of the joint.

## Conclusions

In spite of the fact that for decades it was considered that osteoporosis and arthrosis were mutually exclusive diseases, in the last few years the possibility has been indicated that both processes coexist, and that they even bear a direct relationship on each other. However, the analysis of the possible relationship between the two processes is problematic due to various factors, some of which have been suggested in different studies[17,28,35,53,54]. Firstly, it is possible that there are different patterns of association as a function of the location of the arthrosis. Thus, when the arthrosis affects load-bearing joints, essentially the hip and the knee, a higher BMD is usually found, which in spite of this does not appear to protect the arthrosic patient against the risk of fracture. Something similar occurs in patients with spondyloarthrosis, which presents a higher risk of vertebral fracture. On the other hand, in some cases of arthrosis in peripheral joints, such as in the hands, it is not unusual to find reduced BMD, locally or overall.

Secondly, along with methodological aspects, the influence of certain confusion variables such as

race, body weight, physical activity or alcohol consumption should be taken into account, which may explain, in themselves, the inverse relationship which has been reported between the two entities.

Thirdly, on occasion there may be certain circumstances which influence both processes, such as, for example, estrogen deficiency, a well-known risk factor of osteoporosis, which also appears to contribute to the degeneration of articular cartilage in some experimental models, or the pain of arthrosis of the hip, which may diminish physical activity and increase rolling gait, with the consequent reduction in bone mass and a higher propensity to falls.

Lastly, although not the object of this review, the possible interaction between environmental and genetic factors, which may cause different levels of expression of the genetic susceptibility to suffer one or other disease, should be considered.

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