



## Editorial

### Osteoimmunology, Osteorheumatology or Rheumatology Alone?☆

#### ¿Osteoimmunología, osteo-reumatología o reumatología sin más?

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#### Osteoimmunology

In 2000, Joseph Lorenzo, Yongwon Choi, Mark Horowitz and Hiroshi Takayanagi proposed a new multidisciplinary field of scientific knowledge, which they called osteoimmunology, the content of which would revolve around the idea that the immune and skeletal systems interact, and thus are involved in the pathophysiology of bone diseases.<sup>1</sup> The first of a long list of experiments that supported this relationship showed that peripheral blood monocyte culture supernatant of healthy individuals contained a phytohemagglutinin-stimulated mediator called osteoclast activating factor,<sup>2</sup> later identified as interleukin-1 (IL-1).<sup>3</sup> Later, it was observed that both tumor necrosis factor (TNF) and IL-6 also induce bone resorption.<sup>4,5</sup> Finally, the process of differentiation of osteoclasts, cells responsible for bone resorption from hematopoietic precursors stimulated with colony stimulating factor and macrophage RANKL, was described, as well as the acceleration of osteoclastogenesis by proinflammatory cytokines such as IL-1, TNF and IL-6 in the presence of RANK-L. Subsequently, new developments, beautifully described by Santos and Luis Castañeda Arboleya in this issue of REUMATOLOGÍA CLÍNICA, have been incorporated into the scientific expertise in this line of research, with many exciting discoveries ranging from intracellular signaling through intercellular communication, to understanding the mechanisms of specific injuries such as bone erosion in rheumatoid arthritis or bone metastases cancer.<sup>6</sup> In fact, many of the processes involved in the relationship between the immune system and bone constitute therapeutic targets for the development of new pharmacological interventions.

From a more global and not strictly scientific perspective, osteoimmunology fits well to a double need, on one hand stimulating the development of a field of scientific knowledge and, on the other, providing knowledge. In fact, these same scientists launched in 2006 the International Conference on Osteoimmunology. The idea spread quickly, although with different acceptance rates, as

for some scholars it fits perfectly within the current limits of our specialty. While it is true that the book published by these four authors, *Osteoimmunology: Interactions of the Immune and Skeletal Systems. A Promising Bridge Between the immune and skeletal systems*, is packed with scientific content, so it happens that around such initiatives, lobbyists are generated.<sup>1</sup>

#### Joints and Bone Are Injured in Autoimmune Diseases

Below, we will discuss the reasons that may favor the expansion and consolidation of this proposal. Some are difficult to compress at present, especially for younger readers. We will start from a concrete example: rheumatoid arthritis, which provides an excellent opportunity to understand what the concept of osteoimmunology is and why it has developed. During the first half of the twentieth century, the disease was characterized by progressive and irreversible deterioration of the joints, while treatment depended largely on rehabilitative and physical therapies, there was no really effective drug alternatives. That is, a chronic disease of the musculoskeletal system condemning patients to the spa and disability.

In 1951, Jiménez Díaz et al. published a series of articles that showed the results of treatment with nitrogen mustard in patients with rheumatoid arthritis, as well as a research strategy which was very modern for its time.<sup>7–10</sup> This contribution was a radical change of the vision we had of the disease.<sup>7</sup> Using for the first time immunosuppressive therapy framed this disease in the field of “immuno-allergic” diseases and, from this perspective, it became a treatable disease. Parenthetically, we would like to emphasize a curious fact that should make us think, it being that Spanish rheumatologists have never really been aware of the enormous importance of this contribution to the knowledge of the disease. So much so, that it was a line of research that died without taking off in Spain, but as we all know, triumphed in rheumatology.

Another consequence of this conceptual shift is that one came to think of rheumatoid arthritis as a disease of the synovium and joint, forming the rest of the pathogenesis, especially concerning what happened to the bone, an uninteresting complication from the academic point of view and unnecessary from a therapeutic one. In every way, a failure of the rheumatologist. So, we drifted away from the bone and cartilage, and to the autoimmune diseases without considering the bone. The injury in these tissues was like a sentence with no academic interest.

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Despite this, diarthrodial joints are composed of a synovial membrane, cartilage and subchondral bone, anatomical structures involved in the pathogenesis of all chronic joint diseases. Furthermore, the autoimmune inflammatory diseases not only affect the subchondral bone, but the entire skeleton of the patient. Currently, it is widely accepted that the immune system is involved in the functioning of bone metabolism. Bone homeostasis is largely dependent on remodeling sites and is regulated by immune mechanisms, particularly in situations of pathological activation. Otherwise it makes no biological sense: how is that a system that assists in the functioning of all body tissues was not going to do so in the bone? But in this approach lies a fundamental concept: both the bone and cartilage are living tissues, biologically active, although with operating characteristics derived from their unique structural features.

### **The 2 Components of a Term: Bone on One Side. Immunology Rheumatology and Inflammation on the Other?**

Probably before you can answer that question rigorously we should try to answer the following ones.

- What is the immune response and how does it fit in chronic inflammation? How is innate immunity integrated into this system?
- How should we define the inflammatory response at the cellular level, for example, in chondrocytes or osteoblasts?
- Do tissue damage effector cells of uncalcified cartilage, such as synovial B cells, have a profile similar to the activation and response of osteoclasts?
- Can we say that the bone can become swollen because there is an increase in remodeling?

The joint has a subtle biological interface separating two kinds of tissues with completely different structural features: the bone and the cartilage, on one hand, and the synovial membrane, on the other. When we speak from the synovial standpoint we speak of autoimmune arthritis, and when we do it from the bones' point of view, we talk about osteoimmunology. Obviously, in reality, these are interpretations of the same pathological phenomenon that lead to a single outcome. Without this view, the absence of studies on the effect of mechanical loading on the modulation of immune-related bone is understandable.

To better encompass this field of knowledge with a name more consistent with reality, perhaps we could have resorted to the term osteo-rheumatology, reflecting the biological involvement of bone, cartilage and other periarticular tissues in the pathophysiology of all chronic arthropathies, including of course, those of degenerative origin. Obviously, this field would be immersed in our specialty.

In conclusion, osteoimmunology or osteo-rheumatology are proposals that facilitate the integration of knowledge that, probably for historical reasons, were unnecessarily apart. Not only does it explain the relationship between immunity and bone, but, more importantly, enables a holistic understanding of the disease. In this way, it allow us to better explain the pathogenesis of our patients and allows us to apply more effective treatments. Despite this, in no case does osteoimmunology represent a separate field of knowledge. On the contrary, it closes a cycle, which ultimately ends with the statement that rheumatic diseases are essentially biological-mechanical diseases.

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