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EDITORIAL

Osteo-Immunology and Hip Fractures

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Bone loss in the elderly is associated with fractures and thus a clinically relevant topic, but the underlying mechanism is still not fully elucidated. Endocrinologists unravel the hormonal aspects, geriatricians focus on senescence, and rheumatologists work on the role of systemic inflammation. Before the introduction of biologic disease modifying treatments, both local and generalized bone loss occurred in patients with active RA and high levels of systematic inflammation, leading to local erosions and fractures [1]. In 2006, Schett et al. showed in a population-based study that CRP levels are a significant and independent risk predictor of fractures, demonstrating the tight interplay between low-grade inflammation and bone turnover [2]. The association between inflammatory markers and hip fractures was recently confirmed in both men and women. [3, 4].

These studies were drivers in the development of osteoimmunology, an interdisciplinary field that explores the interaction of inflammatory cells and cytokines with bone cells and regulators of the skeletal system. The field of osteoimmunology is supposed to build a conceptual bridge between bone metabolism and the immune system, not only for better understanding but also for initiating new therapeutic approaches [5].

With this background, the study published in the present edition of Calcified Tissue International by Elam is very welcome [6]. Briefly, in a population-based study in US men and women 65 years and over, with a median follow-up of 9.7 years, the occurrence of 259 hip fractures was observed in 1928 individuals with at least one available innate and adaptive immune cell subset at baseline. Obviously, an impressive large study; other strengths of the study are the careful collection of hip fractures, by continuous follow-up with telephone calls each six months, and the predefined primary analysis of natural killer (NK) cells, γδ T cells, T helper 17 (Th 17) and differentiated/senescent CD4 + CD28 T cell subsets (in total 25 immune cell phenotypes were measured).

What about the results? Since there were no significant associations in the combined analysis of men and women, one can argue that the results of this study were "negative". On the other hand, there are well-known skeletal differences in men and women: there are hormonal differences (estrogen deficiency!), but maybe also differences in low-grade inflammation and senescence. Interestingly, it was observed that Th17 cells were positively associated with hip fractures in women (HR 1.18, 95% c.i. 1.01–1.39), which is in line with earlier data showing that IL-17 is associated with stimulated osteoclastogenesis and inhibited bone formation. The relationship between Th17 cells and hip fractures was not found in men, probably because estrogen deficiency is a strong stimulator of bone loss through Th17 cells (in postmenopausal women) [7].

Secondly, NK cells were inversely associated with hip fractures in women, which was unexpected, since earlier data has shown that NK cells promote osteoclast development and activity in preclinical and animal models [8]. Thirdly, in men, γδ T cells were also inversely associated with hip fractures, also somewhat unexpected. The authors suggest that higher peripheral blood proportions of γδ T cells are associated with lower numbers at the local bone tissue level.

Can the negative results in the combined group of men and women be explained by flaws in the design of the study? At this stage it is worth highlighting that above mentioned studies only showed associations between immunology markers/immune cells and osteoclast activity, bone mineral density or bone strength. However, there are many BMD independent risk factors leading to an increased hip fracture risk. The analysis adjusted for several potentially confounding factors (age, sex, race, education level, BMI, clinic, education level, alcohol, smoking, medication), but not for vertebral fractures and not for falls. Vertebral fractures are

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strongly related to bone loss, but require imaging techniques; fall events are strongly related to hip fractures and could have been easily collected during the phone calls about hip fractures each 6 months. Other confounders, such as neuromuscular or visual impairments and genetics, are also not documented. Finally, how reliable is a one-time moment of immune cells in an observational study of 9.7 years? That is not known, but earlier data suggest that immune cell phenotypes are relatively stable over 18 months.

How to interpret the results? One conclusion is that the relationship between immunological cell subsets and hip fractures is probably not very strong.

The most interesting data are the association of Th17 cells and hip fractures. This is in line with earlier clinical data from a posthoc analysis in patients with axial spondyloarthritis: IL17 inhibition led to an increase in spine BMD with 4.7% over 2 years, but only a 0.5% increase at the total hip, and no relevant effects on bone turnover markers were observed. [9].

Data on NK cells and γδ T cells are both also significant, but positive associations were expected, while negative associations were found. One option is to regard these associations as “’wrong”” or “”chance finding””, but then we do not learn anything from these exciting data. Another option is to admit that we cannot fully understand (yet) the differences between the data from preclinical and animal models and the human data from the study by Elam et al. Animal models [10], in particular transgenic mice, are powerful to functionally evaluate the importance of T cells and NK cells, by eliminating key genes (e.g. IL-17 RA) or even cells and test the effects on bone homeostasis or models of estrogen deficiency [11]. Conditions in animals are rather defined which might not reflect the various conditions in large cohorts. On the other hand in humans, analysis is in general naturally restricted to circulating blood cells which may not entirely reflect the presence of these cells in bone tissue.

So, in our opinion, more data are needed, both in preclinical models as in humans, to unravel the osteoimmunological aspects of bone loss in the elderly, with the future perspective to treat our patients better.

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