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EDITORIAL

The Enigma of Vitamin D Role in Inflammation

Vitamin D is a widely studied molecule, but several aspects of its biologic behaviour remain unclear. Despite having been considered for decades solely as a co-actor of the bone metabolism regulation, multiple experimental observations have suggested a role in different fields of human physiology [1]. Notably, numerous authors attributed to vitamin D key functions in the regulation of the immune system [2 - 12], hence revealing its potential contribution in the management of inflammatory diseases [13 - 22].

However, as well as for other promising molecules under investigation, a significant gap between the strength of the *in vitro* data and the weakness of the *in vivo* observations still exists. There are several reasons beyond this discrepancy: for instance, experimental conditions *in vitro* cannot replicate the complex regulation of the vitamin D-dependent pathways *in vivo*; moreover, vitamin D concentrations used *in vitro* are generally significantly higher than those physiologically measured in human subjects. To date, the real and actual impact of the vitamin D status on inflammation *in vivo* is still an enigma. Consequently, whether or not vitamin D plays a relevant role in the development and management of inflammatory diseases is still a matter of debate. If, on the one side, we should not neglect vitamin D potentialities, on the other side, we must avoid considering it a "panacea", as this misinterpretation might lead to overtreatment with direct and indirect relevant costs [23, 24].

A large-scale screening and supplementation strategies for therapeutic indications other than the maintenance of bone homeostasis are currently not supported by the available evidence, and their clinical advantage and cost-effectiveness are doubtful.

In this special issue, contributions from eminent figures in this field have been gathered to try to elucidate what we already know and what is new about vitamin D and inflammation.

At first, Trombetta and colleagues [25] extensively and comprehensively revised the current knowledge about the *in vivo* and *in vitro* vitamin D activity on the immune system regulation and its implications for the development of autoimmune diseases. To deepen the insights on specific pathological conditions, Nerviani *et al*. [26] reviewed the relevant literature about the impact of the vitamin D status on the clinical course of Systemic Lupus Erythematosus (SLE). In this manuscript, the authors presented the available data assessing the effects of vitamin D on several markers of disease activity, further discussing the evidence supporting a role for vitamin D supplementation in the management of SLE. The specific relationship with the antiphospholipid antibody syndrome has been revised in depth by Gualtierotti and colleagues [27], who also included original data showing the *in vitro* effects of vitamin D supplementation on the endothelial perturbation in this condition.

In the context of inflammatory arthritis, Crotti and colleagues [28] discussed the current evidence about the role of vitamin D in the development of spondyloarthritis; here the authors not only underpinned the discrepancies existing in this field, but also stressed the relevance that vitamin D status seems to have in the occurrence of some critical co-morbidities in the course of systemic inflammatory diseases.

Resulting from the impairment of several biological pathways involved in the bone metabolism, osteoporosis and increased risk of fracture are common in inflammatory arthritis. Bone health and immune system are strictly related, and their complex and intriguing connections are the matter of study of a recently developed field known as "osteoimmunology". In this regards, Sainaghi and Gibbin [29] reviewed the available pieces of evidence supporting the direct implication of the vitamin D status in the development of osteoporosis in patients affected by inflammatory arthritis.

Furthermore, cardiovascular diseases are classical and severe complications of chronic inflammatory disorders, widely accounting for the increased mortality observed in these conditions. The atherogenic profile related to the chronic inflammatory state largely contributes to the increased cardiovascular risk; nevertheless, as broadly discussed by Bellan and Marzullo [30] in their manuscript here enclosed, vitamin D seems to play a critical role in the regulation of the glucose metabolism, which is a primary determinant of the cardiovascular risk. If this link is generally valid in patients affected by Type 2 Diabetes, vitamin D appears to be even more relevant in Type 1 Diabetes, in which the aberrant activity of the immune system is essential. The impact of vitamin D status on Type I Diabetes development and management has been discussed here by Savastio et al. [31]. Finally, original data about the influence of the antiviral treatment on the vitamin D/parathyroid hormone axis in chronic hepatitis C have been here presented in the manuscript by Salmi et al. [32].

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