Editorial

Do low vitamin D levels cause problems of waste removal in patients with SLE?

The need for more basic science research


The study by Mok et al. [1] in this issue analyses the effect of vitamin D on the clinical appearance of SLE. They describe that levels of 25-hydroxyvitamin D3 correlate inversely with disease activity and that hypovitaminosis D is associated with pre-menopausal status, dyslipidaemia and the presence of aPLs. However, subclinical atherosclerosis is not associated with low levels of vitamin D.

The epidemiological data in Table 5 [1] highlight a significant association between hypovitaminosis D and SLE. Other autoimmune disorders such as IBD, multiple sclerosis, RA, UCTD and diabetes mellitus type I have also been associated with low levels of vitamin D [2, 3]. In the MRL/pr murine lupus model, supplementation with vitamin D3 significantly reduced proteinuria and increased longevity [4].

The higher prevalence of some autoimmune diseases in people living in high-latitude countries is probably attributed to their reduced exposure to sunlight compared with those living in low-latitude countries [5] and consequently is most likely to be related to hypovitaminosis D [6]. The higher incidence of SLE in African-Americans cannot be associated simply with genetic factors because of the lower incidence of the disease among black individuals from West Africa. However, higher skin pigmentation along with lower amounts of exposure to sun might contribute to the decreased concentrations of serum vitamin D in the black population living in North America. Hypovitaminosis D is also common in young and post-menopausal Arabian women [7], who are known to be exposed to very low doses of sunlight because of cultural reasons and traditional clothing. Consequently, inadequate levels of vitamin D are highly prevalent in Saudi Arabian females, especially in patients with SLE [8].

7-Dehydrocholesterol is the precursor to vitamin D3 and forms cholecalciferol only after being exposed to ultraviolet (UV) type B radiation in the skin. Cholecalciferol can also be ingested orally and is then hydroxylated in the liver to become calcifediol (25-hydroxyvitamin D3), the main circulating form of vitamin D. Next, calcifediol is again hydroxylated, but this time in the kidney, and becomes calcitriol (1,25-dihydroxyvitamin D3), the active form of vitamin D3. The most prominent and well-known function of vitamin D is regulation of calcium homeostasis by its interaction with the parathyroid, kidney and intestinal tissues [9].

In the immune system, vitamin D3 inhibits cell proliferation of Th1 in CD4 T cells and production of Th1 cytokines. Production of the Th17 stimulating factor IL-6 is also inhibited by vitamin D3. In B cells, vitamin D3 inhibits secretion of antibody and production of autoantibody. In vitro, vitamin D3 stimulates phagocytosis and killing of bacteria by macrophages, but it suppresses the antigen-presenting capacity of these cells and that of dendritic cells. Vitamin D is also considered a potent blocker of dendritic cell differentiation and of IL-12 secretion. Many of these immunosuppressive effects are mediated by the interaction of the hormone with its nuclear receptor, the vitamin D receptor (VDR), which regulates the expression of genes in vitamin D responsive tissues [2].

Taking into consideration the epidemiological data and potential immunosuppressive roles of vitamin D3, it is tempting to speculate about the role of vitamin D in the aetio-pathogenesis of SLE. Active phagocytosis with anti-inflammatory and immunosuppressive consequences is the main reason for the clearance of apoptotic cells in multicellular organisms [10]. SLE is believed to be triggered and aggravated by an impaired clearance of apoptotic cells. The disease-associated chronic inflammation is sustained by the accumulation of post-apoptotic debris in various tissues. Several in vivo and in vitro observations suggest an inefficient removal system of dying cells in patients with SLE as mechanistically related to both aetiology and pathogenesis of SLE. A reduced clearance of dying cells by tingible body macrophages causes accumulation of secondary necrotic cells in germinal centres (GCs). This cellular debris is able to activate the classic complement pathway and C3b-coated chromat in may be captured by follicular dendritic cells (FDCs) and exposed on their surfaces. At this point, GC chromatin-reactive B cells that had been accidentally generated by somatic mutations receive short-term survival signals and are now able to leave the GC and enter the mantel zone, where they finally get long-term survival signals from autoreactive CD4 Th cells (Fig. 1). Consequently, tolerance to nuclear self-antigens is challenged and finally broken [11]. Vitamin D is required for a proper function of phagocytes. If low, impaired clearance in GCs of apoptotic cells can lead to the accumulation of cellular and nuclear debris. Debris binds complement and can be presented by
FDCs. Autoreactive B cells generated by stochastic mutations recognizing nuclear autoantigens may be rescued from deletion. Rarely, autoreactive B cells may then obtain further stimulation from autoreactive T cells in the mantle zone. Consequently, some autoreactive B cells survive, proliferate and differentiate into plasma cells producing anti-nuclear autoantibodies, a serological hallmark of patients with SLE.

Whether vitamin D3 deficiency seems to worsen the clearance of apoptotic cells in patients with SLE and whether this mechanistically accounts for disease flares deserves the attention of further basic research. Considering these robust epidemiological data, one might believe that vitamin D deficiency plays a pivotal role in the multifaceted aetiopathogenesis of autoimmunity that deserves further scientific research to pinpoint the mechanisms of action of vitamin D in the phagocytosis and clearance of dying cells.

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Luis E. Munoz1, Martin Schiller2, Yi Zhao1,3, Reinhard E. Voll1,4, Georg Schett1 and Martin Herrmann1

1Department for Internal Medicine 3, Erlangen University Hospital, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, 2Department of Medicine V, University of Heidelberg, Heidelberg, Germany, 3Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, China and 4Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Germany.

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Correspondence to: Martin Herrmann, Department for Internal Medicine 3, Erlangen University Hospital, Friedrich-Alexander University of Erlangen-Nuremberg, Krankenhausstr. 12. 91054, Erlangen, Germany.

E-mail: Martin.Herrmann@uk-erlangen.de

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