Autoimmunity Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Vitamin D and juvenile systemic lupus erythematosus: Lights, shadows and still unresolved issues

Stefano Stagi [a,*], Donato Rigante [b]

[a] Health Science Department, University of Florence, Anna Meyer Children's University Hospital, Florence, Italy
[b] Institute of Pediatrics, Fondazione Policlinico Universitario "A. Gemelli", Università Cattolica Sacro Cuore, Rome, Italy

ARTICLE INFO

Article history:
Received 8 November 2017
Accepted 13 November 2017
Available online xxxx

Keywords:
Vitamin D
Systemic lupus erythematosus
Juvenile systemic lupus erythemathosus
Lupus nephritis
Bone density
Bone metabolism
Osteoporosis
Bone fractures

ABSTRACT

Systemic lupus erythematosus (SLE) and juvenile SLE (jSLE) are autoimmune disorders naturally associated with several genetic, environmental, hormonal, and immunological contributing factors. It has been assumed that vitamin D deficiency may have a role in the immune activation of patients with SLE and play an active part in many comorbidities and even complications. A host of clinical studies suggested that vitamin D exerts inhibitory effects on many immunological abnormalities associated with SLE, also in children and adolescents, while different reports have hypothesized that vitamin D may be associated with accelerated cardiovascular disease in SLE. This review updates and summarizes the information related to the immunoregulatory effects of vitamin D and its importance in jSLE, discusses the innumerable correlations between vitamin D and disease activity, including clinical expression and gene polymorphisms of vitamin D receptor as well as the recommendations for vitamin D supplementation in these patients. Despite the excitement raised by many data obtained about vitamin D and its influence on several aspects of the disease, further well-designed perspective trials are required to define the exact role that vitamin D may have in the management of both SLE and jSLE.

Contents

1. Introduction . . . 0
2. The basic principles of vitamin D metabolism in the body and in the immune system . . . 0
3. Vitamin D deficiency in patients with systemic lupus erythematosus . . . 0
4. The role of genetics in vitamin D balance and systemic lupus erythematosus . . . 0
5. Vitamin D deficiency and comorbidities of systemic lupus erythematosus, with emphasis to bone health . . . 0
6. Vitamin D, immune system and infectious diseases in systemic lupus erythematosus . . . 0
7. Vitamin D and cardiovascular disease in systemic lupus erythematosus . . . 0
8. Systemic lupus erythematosus and fatigue: a role for vitamin D? . . . 0
9. Vitamin D supplementation in systemic lupus erythematosus . . . 0
10. Conclusive remarks . . . 0
Declaration of interest . . . 0
Funding . . . 0
References . . . 0

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder characterized by heterogeneous clinical manifestations of variable severity with involvement of skin, joints, blood cells, brain, kidney, though every organ of the human body might be involved [1–3]. In 15–20% of patients the disease starts in childhood or adolescence, being named juvenile-onset systemic lupus erythematosus (jSLE): this peculiar form of the disease requires long-term and often aggressive treatments, because clinical presentation is frequently more severe than in adults with SLE or often characterized by life-threatening involvement of kidney

* Corresponding author.
E-mail address: stefano.stagi@unifi.it (S. Stagi).

https://doi.org/10.1016/j.autrev.2018.01.004
1568-9972/

Please cite this article as: Stagi S, Rigante D, Vitamin D and juvenile systemic lupus erythematosus: Lights, shadows and still unresolved issues, Autoimmun Rev (2018), https://doi.org/10.1016/j.autrev.2018.01.004

and central nervous system [4]. The autoimmune mechanisms responsible for SLE and jSLE and numerous agents contributing to their onset and progression are not completely clarified, but both genetic background and environmental factors have a clear position in the pathogenesis [5]. Tipically, SLE and jSLE patients develop T and B cell-mediated autoimmune responses against a host of self-antigens, mostly intracellular [6]. This is the precondition causing the development of immune complexes, whose deposition in many tissues provokes local inflammation and tissue damage with progressive multiple clinical phenomena [3,7].

In the last decade, vitamin D has attracted the attention of many clinicians beyond its conventional role related to bone and calcium homeostasis: vitamin D receptors have been discovered in immune cells, including antigen-presenting cells, natural killer cells, and B and T lymphocytes [6,8], leading to hypothesize a potential role of vitamin D in the regulation of immune responses in different autoimmune disorders [8]. Vitamin D deficiency has also been associated with the pathogenesis of SLE [9,10], and its supplementation seemed to improve disease outcome in an animal model of SLE [11]. Indeed, vitamin D deficiency may be correlated with impaired bone mass achievement and development of osteoporosis as well as with bone fractures in both SLE [12] and jSLE [13,14].

Aim of this review is to focus on the most recent data from the medical literature regarding the relationship between vitamin D, SLE and mostly jSLE. Studies have been searched from the electronic databases of PubMed and Cochrane Library until September 2017. The retrieving words have been “vitamin D”, “vitamin D receptor (VDR)” and “systemic lupus erythematosus” (both SLE and jSLE) to enter the databases; additional reports were identified and analyzed through the specific references cited in the retrieved articles.

2. The basic principles of vitamin D metabolism in the body and in the immune system

Vitamin D is a steroid hormone with a well-known master role in calcium metabolism and bone homeostasis [15], existing in two fat-soluble physiological forms: one of vegetable origin (vitamin D_2 or ergocalciferol) and one of animal origin (vitamin D_3 or cholecalciferol) [15–17]. The primary source (80%) is synthesis of vitamin D_3 in the skin after exposure to ultraviolet B light (~280-to-315 nm), while approximately 20% of vitamin D is exogenously acquired from foods, in particular oily (fatty) fish, or supplements [17–19]. Vitamin D_3 is then hydroxylated at carbon 25 in the liver to 25 hydroxyvitamin D (25OH-vitamin D or calcifediol), a metabolically inactive form which is the major circulating vitamin D in the blood, then further hydroxylated by 1 α hydroxylase to the active form, 1,25 dihydroxyvitamin D or 1,25 $(OH)_2D_3$ (also termed calcitriol). This last step occurs predominantly, if not exclusively, in the proximal convoluted tubule cells of the kidney as well as in cells of the immune system, that may have the ability to produce $1,25(OH)_2D_3$ in a paracrine or autocrine manner [17–19]. Synthesis of $1,25(OH)_2D_3$ is tightly regulated and primarily stimulated by serum parathyroid hormone (PTH), then its role is mostly directed to obtain elevation of both plasma calcium and phosphorus. In fact, for first, $1,25(OH)_2D_3$ operates directly on the enterocytes of the small intestine to stimulate calcium and phosphorus absorption from the lumen into the plasma compartment [17–19]. $1,25(OH)_2D_3$ plays also a crucial function in the mobilization of calcium from bone tissue, in combination with PTH, as well as it markedly increases renal reabsorption of calcium in the distal tubule [17–19]. Moreover, $1,25(OH)_2D_3$ regulates the transcription of several inflammatory cytokines [20].

At the cellular level, $1,25(OH)_2D_3$ binds to the intracellular vitamin D receptor (VDR), belonging to the superfamily of nuclear hormone receptors, which, similarly to corticosteroids, thyroid hormone, and retinoid receptors, modulate gene transcription in many target tissues [16–19]: this receptor is expressed by a variety of cells, including the epithelium of small bowel and renal tubules, osteoblasts, osteoclasts, hematopoietic cells, monocytes, dendritic cells, lymphocytes, epidermal cells, pancreatic cells, myocytes, and even neurons [16–19]. After ligand binding the VDR forms a heterodimer with the retinoid X receptor and binds to vitamin D_3 response elements, recruiting a number of nuclear coactivator or corepressor proteins, resulting in the expression or trans-repression of specific gene products [16]. After the discovery of VDR in immune cells, including antigen-presenting cells, natural killer cells, and B and T lymphocytes, a large interest has been focused on vitamin D and, in particular, on its role in the regulation of different immune responses [8,17]. The highest VDR concentration was discovered in immature immune cells of the thymus and in mature CD8 T lymphocytes, regardless of their activation state [18]. Therefore, vitamin D may contribute physiologically to the autocrine and paracrine regulation of both innate and adaptive immunity pathways [21]. Numerous data support the hypothesis that $1,25(OH)_2D_3$ enhances the innate immune response, whereas it exercises an inhibitory effect on the adaptive immune system, ameliorating the T cell receptor-induced T cell proliferation [22,23], promoting the generation of $CD4^+/CD25^+$ T regulator cells (T-regs), and specifically inhibiting Th1 cell proliferation [24,25] with a shift toward a Th2 response [26,27]. In addition, vitamin D has also direct effects on B cell responses, inducing apoptosis, inhibition of B cell proliferation, generation of B memory cells, plasma cell differentiation as well inhibition of immunoglobulin production [28].

In general terms, $1,25(OH)_2D_3$ inhibits the maturation of dendritic cells with the specific inhibition of activation markers, such as major histocompatibility complex class II, and many of the costimulatory molecules, such as CD40, CD80 and CD86 [29]. Finally, $1,25(OH)_2D_3$ downregulates dendritic cell production of interleukin (IL)-12, whereas it increases the production of IL-10, which in turn promotes tolerogenic properties and facilitates induction of T-reg instead of T-effector cells [30]. Overall, the whole bulk of data suggests that vitamin D may have a contributive role to the pathogenesis of different autoimmune diseases, including type 1 diabetes mellitus [31], multiple sclerosis [32], rheumatoid arthritis [33] and SLE [34–38].

3. Vitamin D deficiency in patients with systemic lupus erythematosus

In 1979 low levels of vitamin D were reported in patients with SLE [39] and, afterwards, the disease has been potentially linked to vitamin D deficiency [13,37,40–51]. Prevalence of vitamin D insufficiency has been estimated between 38 and 96% in SLE [37,47,52–57], while in the general population it ranges from 8 to >30% [37,47,54–60]. These results are quite similar also for patients with jSLE, although lower 25(OH)D levels have been frequently observed, with reduced total calcium or higher levels of phosphate and PTH [14]. Many factors may contribute to vitamin D deficiency and insufficiency in both SLE and jSLE patients, mainly sun avoidance, use of sunscreens or drugs interfering with vitamin D metabolism, such as corticosteroids, hydroxychloroquine, and immunosuppressants. In the cutaneous lupus erythematosus (CLE) vitamin D deficiency can be even highlighted in any season of the year [61].

Most studies, showing a significant association between vitamin D insufficiency and SLE, were carried out at different latitudes both in European and non-European countries: despite this geographical heterogeneity, a clear demonstration of insufficiency (<30 ng/ml) or deficiency (<20 ng/ml) of vitamin D was found, and this could be due to the fact that patients avoid sunlight triggering dermatological or systemic flares, as clearly shown for patients with CLE [62]. This may be even worsened by the recommendation to apply sunscreen when outdoors, which lowers the interaction with sunlight and impairs the achievement of optimal vitamin D levels [63,64]. Furthermore, SLE patients frequently present kidney involvement, with subsequent disrupted 1-hydroxylation of vitamin D into its active form, and indeed several data have shown that patients with active SLE and lupus nephritis (LN) have significantly lower levels of vitamin D. This suggests that glomerulonephritis may be a significant predictor of vitamin D deficiency in SLE [54]. Other contributing factors are higher therapeutic

Please cite this article as: Stagi S, Rigante D, Vitamin D and juvenile systemic lupus erythematosus: Lights, shadows and still unresolved issues, Autoimmun Rev (2018), https://doi.org/10.1016/j.autrev.2018.01.004