REVIEW

Autoimmune disease and interconnections with vitamin D

Jane Fletcher[1,2], Emma L Bishop[3], Stephanie R Harrison[4], Amelia Swift[2], Sheldon C Cooper[5], Sarah K Dimeloe[3], Karim Raza[6] and Martin Hewison[7]

[1]Nutrition Nurses, University Hospitals Birmingham NHS Trust, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, UK
[2]School of Nursing, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, UK
[3]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
[4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds, UK
[5]Gastroenterology Department, University Hospitals Birmingham NHS Trust, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, UK
[6]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[7]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

Correspondence should be addressed to M Hewison: m.hewison@bham.ac.uk

Abstract

Vitamin D has well-documented effects on calcium homeostasis and bone metabolism but recent studies suggest a much broader role for this secosteroid in human health. Key components of the vitamin D system, notably the vitamin D receptor (VDR) and the vitamin D-activating enzyme (1α-hydroxylase), are present in a wide array of tissues, notably macrophages, dendritic cells and T lymphocytes (T cells) from the immune system. Thus, serum 25-hydroxyvitamin D (25D) can be converted to hormonal 1,25-dihydroxyvitamin D (1,25D) within immune cells, and then interact with VDR and promote transcriptional and epigenomic responses in the same or neighbouring cells. These intracrine and paracrine effects of 1,25D have been shown to drive antibacterial or antiviral innate responses, as well as to attenuate inflammatory T cell adaptive immunity. Beyond these mechanistic observations, association studies have reported the correlation between low serum 25D levels and the risk and severity of human immune disorders including autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, type 1 diabetes and rheumatoid arthritis. The proposed explanation for this is that decreased availability of 25D compromises immune cell synthesis of 1,25D leading to impaired innate immunity and over-exuberant inflammatory adaptive immunity. The aim of the current review is to explore the mechanistic basis for immunomodulatory effects of 25D and 1,25D in greater detail with specific emphasis on how vitamin D-deficiency (low serum levels of 25D) may lead to dysregulation of macrophage, dendritic cell and T cell function and increase the risk of inflammatory autoimmune disease.

Key Words
- vitamin D
- inflammation
- autoimmune
- T cell
- dendritic cell

Endocrine Connections (2022) **11**, **e210554**

Introduction

Vitamin D and its metabolites are secosteroids that are derived primarily from the action of UV light on skin to photolytically convert epidermal 7-dehydrocholesterol to vitamin D3 (cholecalciferol). Vitamin D3 can also be obtained from some animal-based food sources and vitamin D2 (ergocalciferol) can be obtained from some non-animal foods. For the remainder of this review vitamin D3 and vitamin D2, and their metabolites will be referred to collectively as vitamin D. As outlined in Fig. 1, the physiological actions of vitamin D metabolites are dependent on further metabolic steps (1). The first occurs in the liver via the enzyme vitamin D-25-hydroxylase

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

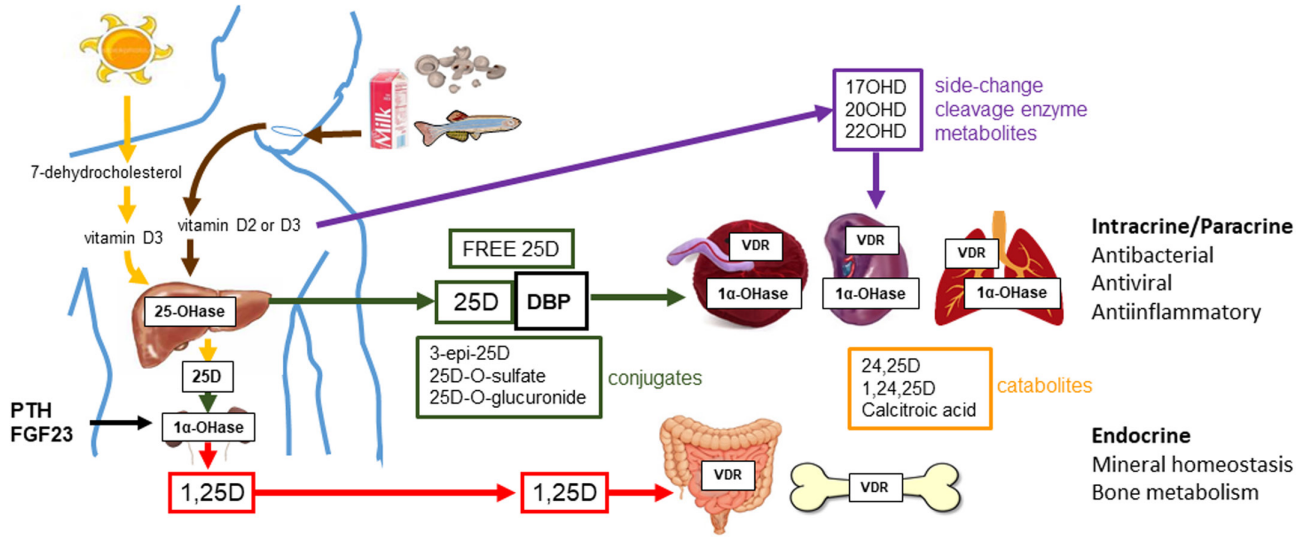

Figure 1
Vitamin D metabolism and the 'vitamin D metabolome'. Schematic showing the synthesis of vitamin D (vitamin D3 and vitamin D2) and different subsequent metabolic pathways: synthesis of 25-hydroxyvitamin D (25D) from vitamin D by 25-hydroxylase (25-OHase); synthesis of 17-hydroxyvitamin D (17OHD), 20S-hydroxyvitamin D (20OHD), and 22-hydroxyvitamin D (22OHD) from vitamin D by the side-chain cleavage enzyme; synthesis of 1,25-dihydroxvitamin D (1,25D) from 25D by 1α-hydroxylase (1α-OHase); synthesis of 24,25-dihydroxvitamin D (24,25D) from 25D by 24-hydroxylase (24-OHase); synthesis of 1,24,25-trihydroxvitamin D (1,24,25D) from 25D by 24-OHase; synthesis of calcitroic acid from 1,24,25D by 24-OHase. 25D (and other vitamin D metabolites) can circulate bound to vitamin D-binding protein (DBP) or unbound (free 25D). Other prominent forms of 25D found in the circulation include 3epi-25D and sulphated and glucuronide forms of 25D. Intracrine synthesis of 1,25D from 25D in tissues such as the placenta, spleen (immune system) and lungs is associated with immunomodulatory effects. Endocrine synthesis of 1,25D in the kidneys is associated with mineral homeostasis and bone health.

(25-OHase) to generate 25-hydroxyvitamin D (25D). While this is recognised as the main circulating form of vitamin D, it has also been reported that sulphate and glucuronide conjugated forms of 25D are present in serum in abundance and may represent an additional substantial reservoir of 25D (2). Vitamin D3 and D2 can be metabolised via the cholesterol side-chain cleavage enzyme to generate several alternative forms of vitamin D, including 20S-hydroxyvitamin D (3).

In classical vitamin D endocrinology, 25D is metabolised to the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25D) via the enzyme 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase), with this activity occurring primarily in the proximal tubules of the kidney under positive and negative control by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) respectively. Binding to its cognate nuclear vitamin D receptor (VDR), 1,25D functions as a steroid hormone to regulate transcription (4) and epigenomic effects (5). In this endocrine setting, 1,25D is thus able to promote the gastrointestinal acquisition of dietary minerals such as calcium and phosphate. 1,25D also plays a key role in stimulating FGF23 expression and suppressing PTH, and also promotes feedback regulation of 25D and 1,25D by stimulating catabolism of these forms of vitamin D to less active metabolites, notably via the enzyme 24-hydroxylase (6). The lipophilic nature of vitamin D metabolites means that they are mainly transported in the circulation by the binding globulin vitamin D-binding protein (DBP). Binding to DBP is particularly important for 25D as renal reabsorption of the DBP-25D complex is essential for the renal synthesis of 1,25D (7). However, in common with other steroid hormones, a small amount of 25D circulates either unbound (free 25D) or bound with low affinity to abundant serum proteins such as albumin. Although small, this fraction of 25D appears to be biologically important as free or bioavailable 25D may be the key form of 25D that is able to preferentially access extra-renal sites of 1α-hydroxylase activity (examples shown in Fig. 1 include the placenta, spleen (representing the immune system) and lungs) (7). The relationship between 25D and DBP supports a role for the free hormone hypothesis in vitamin D physiology, but it has also highlighted the potential importance of non-endocrine actions of 25D and 1,25D. In many extra-renal sites, localised synthesis of 1,25D appears to facilitate endogenous VDR responses that are distinct from the classical endocrine actions of 1,25D. A tissue-specific mode of action for vitamin D appears to be particularly prominent in the immune system, and the

importance of this will be discussed in greater detail later in the current review.

Approximately 50% of the UK population has a risk of 25D-deficiency based on Institute of Medicine parameters (<50 nM serum 25D) (8). This has led to national recommendations for vitamin D supplementation (9). However, current definitions of vitamin D-sufficiency are based on classical endocrine calcium/bone effects and may underestimate the requirements for extra-skeletal actions of vitamin D (10). Importantly this includes immunomodulatory responses linking 25D-deficiency to autoimmune diseases including common chronic inflammatory disorders (11, 12, 13). Furthermore, studies *in vivo* and *in vitro* have demonstrated potent anti-inflammatory actions of 1,25D that affect the major cellular players associated with autoimmune disease (14, 15, 16, 17). Supplementation with vitamin D or its analogues may therefore provide a cheap and safe therapeutic strategy for the prevention and/or treatment of autoimmune disorders but supplementation studies to address this have so far been limited and exploratory. The aim of the current review is to provide an update on the mechanistic basis for the interconnection of 25D and 1,25D with autoimmune disease, and how this informs future strategies for the clinical implementation of vitamin D supplementation.

Vitamin D, innate immunity and antigen presentation

The initial observation linking vitamin D with the immune system was the presence of specific binding sites for 1,25D in cells from the immune system (18). The subsequent identification of the VDR for 1,25D confirmed that this protein is expressed in activated, but not resting, lymphocytes and is ubiquitous in cells from the myeloid lineage such as monocytes and macrophages (19). In parallel with these observations, it was noted that monocytes and macrophages exhibited the ability to metabolise 25D to 1,25D. This 1α-hydroxylase activity was initially observed in macrophages from patients with the granulomatous disease sarcoidosis where it was sufficient to elevate circulating levels of 1,25D in some patients leading to potential hypercalcemia (20). Although immune cell 1α-hydroxylase activity has subsequently been demonstrated for a wide range of inflammatory and granulomatous diseases (21), this does not appear to be an exclusively pathological phenomenon. The ability to metabolise 25D to 1,25D has also been described for normal healthy monocytes/macrophages (22), which show enhanced expression of the genes for 1α-hydroxylase (*CYP27B1)*, and *VDR* following immune stimulation (23). The resulting endogenous synthesis and action of 1,25D have been shown to promote antibacterial (24, 25), and antiviral (26, 27) innate immune responses to infection. The cell-specific nature of these responses, utilising endogenous 1α-hydroxylase activity, means that local levels of 25D rather than active 1,25D, are likely to be the primary determinant of vitamin D-mediated innate immune responses. Given that serum levels of 25D are the principal determinant of vitamin D 'status' in any given individual, the efficacy of antibacterial and antiviral immune responses may therefore be impaired in the setting of 25D-deficiency or enhanced following vitamin D supplementation (28, 29). This facet of 25D/1,25D immunomodulation has attracted much recent interest with respect to the possible impact of serum 25D levels on COVID-19 (30).

The intracrine model described above for vitamin D in monocytes/macrophages and dendritic cells (DC) is not restricted to innate antibacterial and antiviral immunity. In studies that preceded the description of 1α-hydroxylase/VDR-driven antibacterial responses in monocytes/macrophages, we described similar localised metabolism of 25D to 1,25D in monocyte-derived DC leading to the suppression of antigen presentation cell surface antigens on DC such as CD80 and CD86 and concomitant inhibition of T lymphocytes (T cell) proliferation in co-culture analyses (31). Thus, in addition to antibacterial/antiviral innate immune responses, localised synthesis of 1,25D has the potential to influence antigen presentation and subsequent adaptive immune responses by T cells. Also, similar to antibacterial/antiviral responses, the efficacy of the DC intracrine system was enhanced by the maturation of DC using differentiation factors such as lipopolysaccharide and CD40-ligation, which further stimulated 1α-hydroxylase expression and the capacity for 1,25D production (31). To date, most studies of 1α-hydroxylase and VDR expression in innate immunity have utilised monocytes, macrophages and DC-derived *in vitro* from cultures of peripheral blood mononuclear cells. Nevertheless, expression of 1α-hydroxylase (32) and VDR (33) has been reported for DC isolated directly from human tissue, indicating that DC *in vivo* have the potential to utilise 25D to 1,25D metabolism in an intracrine fashion. Vitamin D deficiency or supplementation therefore has the potential to influence antigen presentation and subsequent T cell adaptive immune responses.

Initial observations showed that 25D and 1,25D are able to supress DC maturation (34) and the expression

of cell surface antigens such as CD80 and CD86 that are associated with antigen presentation to T cells (31, 32), leading to impaired T cell activation (31, 35). Subsequent analyses have shown that DC exposed to 1,25D exhibit an immature phenotype that promotes the development of tolerogenic T cells, specifically regulatory T cells (Treg) (36, 37). In DC isolated from human peripheral blood, this response appears to be specific for myeloid DC rather than plasmacytoid DC (pDC), despite both DC sub-sets expressing similar levels of VDR (38). These DC subsets have yet to be assessed for intracrine responses to 25D and so it is unclear whether differential sensitivity to vitamin D status occurs with DC *in vivo*. Moreover, pDC are known to exhibit a tolerogenic phenotype at baseline, and the addition of 1,25D may therefore have little further impact on DC phenotype. The induction of a tolerogenic DC phenotype by 1,25D is associated with phosphorylation and nuclear translocation of NF-κB p65, induction of CCL22, suppression of IL-12 (38) and induction of ILT3 (39). Thus, 1,25D-treated DC exhibit many of the characteristics of conventional tolerogenic DC with the exception of increased expression of CD14 and decreased CD1a (40). Specific markers of 1,25D-induced tolerogenic DC include low secretion of IL-23 and expression of microRNA (miR) 155 and increased expression of miR378. More recent studies using unbiased analyses have described the transcriptomic (41, 42) and proteomic (43) profiles associated with 1,25D-induced tolerogenic DC. This, in turn, has highlighted the importance of cell architecture/morphology (43), and cell metabolism (44, 45) pathways in mediating DC responses to vitamin D, notably with respect to altered DC phenotype. In particular, the promotion of glycolysis, oxidative phosphorylation and the citric acid cycle appears to be essential for 1,25D responses in DC (44). At a functional level, these metabolic changes appear to facilitate changes in fatty acid synthesis that may be pivotal in the regulation of DC morphology and phenotype (46).

T cell effects of 25D metabolism by antigen-presenting cells

After phagocytosis of a pathogen, cells such as macrophages and DC process the resulting antigens and present these, together with major histocompatibility complex (MHC) class II molecules, to CD4+ helper T cells (Th) to stimulate T cell activation and adaptive immune responses. As detailed above and outlined in Fig. 2, DC metabolism of 25D via 1α-hydroxylase and interaction of the resulting 1,25D with endogenous VDR can modulate antigen presentation by promoting a tolerogenic DC phenotype. T cells activated by 1,25D-treated DC exhibit decreased expression of IFNγ and CD154, increased CD152 (35), and increased FoxP3 expression characteristic of Treg (39). Treg can also be induced in the presence of 25D if T cells are activated by antigen-presenting cells such as DC, where there is a capacity for 1α-hydroxylase-mediated synthesis of 1,25D (47). T cells activated in this way also show increased expression of CTLA4 and FoxP3, further highlighting the intracrine pathway for induction of Treg by vitamin D. However, T cells activated by 25D/1,25D-induced tolerogenic DC also exhibit decreased expression of IFNγ, IL-17 and IL-21, indicating suppression of inflammatory Th1, Th17 cells, and follicular B helper T cells (Thf) (47). While all of these cells play an important role in facilitating active adaptive immune responses to a pathogenic challenge, the sustained presence of these cells may lead to unregulated inflammation. It has therefore been proposed that a key immune function of 1,25D is to moderate the magnitude of inflammatory adaptive immune responses, thereby limiting potentially detrimental autoimmune responses (48, 49). It is interesting to note that the intracrine model for indirect regulation of T cells outlined in Fig. 2 appears to be highly dependent on the serum DBP, which is able to limit DC uptake of 25D. In studies *in vitro*, increased concentrations of DBP acted to suppress DC responses to 25D, consistent with the high binding affinity of 25D for DBP (47). This observation is similar to that previously described for monocytes, where antibacterial responses to 25D in monocytes were enhanced in the absence of DBP (50).

Endocrine, paracrine and intracrine mechanisms for T cell responses to 1,25D

The induction of T cell responses, including the Th cells outlined above, takes place within microenvironments in tissues such as lymph nodes where multiple immune cells exist in close proximity. Thus, while 25D appears to utilise an intracrine model to synthesise 1,25D, regulate DC function and indirectly promote anti-inflammatory, pro-regulatory T cell responses, direct effects of both 25D and 1,25D on T cells may also be possible. Activated, but not resting, T cells express VDR (18) and T cells activated using cell-free systems show direct anti-inflammatory, pro-regulatory responses to 1,25D, including induction of CTLA4, FoxP3 and IL-10, and suppression of IFNγ, IL-17 and IL-21 (51). Thus, *in vivo,* it is possible that some T cell responses may occur via conventional endocrine mechanisms utilising circulating 1,25D.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

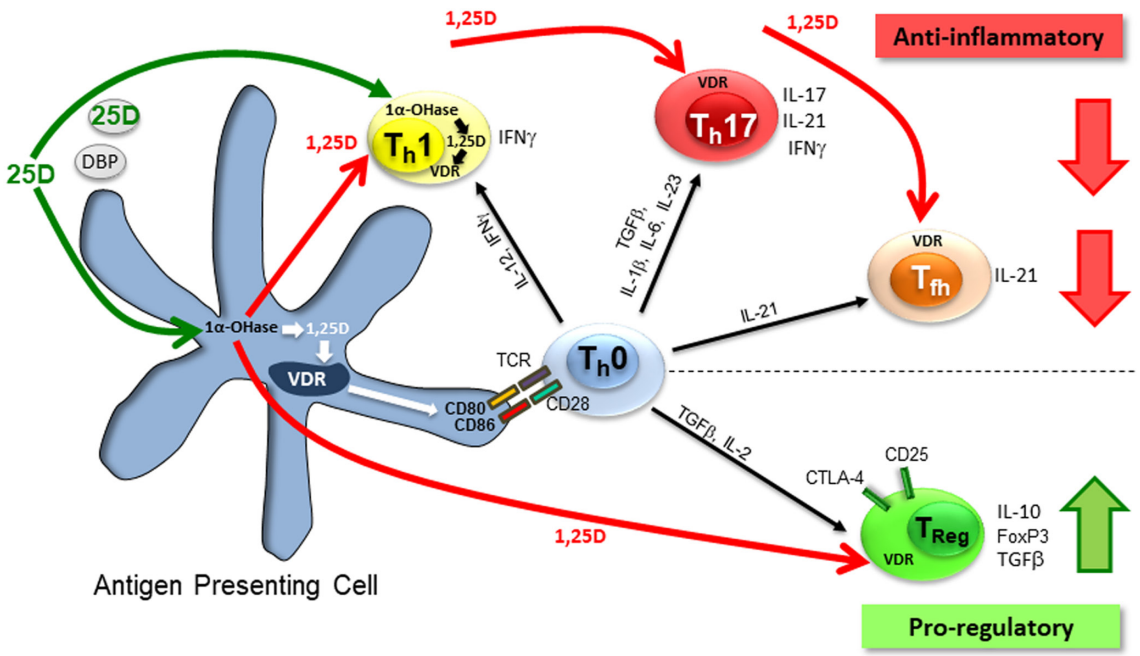

Figure 2
Intracrine vs paracrine effects of vitamin D on helper and regulatory T cell function. Schematic showing the metabolism of 25-hydroxyvitamin D (25D) to active 1,25-dihydroxyvitamin D (1,25D) via 1α-hydroxylase (1α-OHase) activity in antigen-presenting cells such as dendritic cells and T helper (Th)1 cells. Serum transport of 25D by vitamin D-binding protein (DBP) may suppress cellular availability of 25D. Transcriptional response to 1,25D following binding to the vitamin D receptor (VDR) modulates antigen presentation through target molecules such as CD80 and CD86 to influence the activation of quiescent T helper (Th)0 cells to Th1, Th17 , Tfh and regulatory T cells (Treg). These T cell phenotypes require specific cytokines (shown next to arrows). Production of 1,25D by antigen-presenting cells may result in paracrine effects on adjacent VDR-expressing T cells leading to the down or up-regulation of specific T cell cytokines (shown next to the T cell sub-types). Production of 1,25D by Th1 cells may also result in intracrine effects to suppress inflammatory Th1 immunity.

An additional scenario outlined in Fig. 2 is that 1,25D synthesised locally from 25D by DC or monocytes/macrophages can act in a paracrine fashion on adjacent T cells. These effects may also include actions on MHC class I-induced CD8+ cytotoxic T cells which also express VDR and respond to 1,25D (52). Cytotoxic T cells play a key role in mediating the effects of vitamin D on tumour cells and bacterial and viral infections (53). However, it has been reported that CD8+ cytotoxic T cells are not required for the effects of 1,25D in preventing the mouse model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (54), suggesting that Th rather than cytotoxic T cells are the principal adaptive immunity cells required for autoimmunity effects of 1,25D. Interestingly, in mice, cytotoxic T cells may be a more important source of local 1α-hydroxylase expression than murine macrophages (55), raising the possibility of intracrine actions of 1,25D in some T cell populations, and also suggesting that cytotoxic T cells may be an alternative source of paracrine 1,25D. Expression of *CYP27B1* and intracrine responses to 1,25D have also been reported in human cytotoxic T cells (56), but the precise magnitude and function of this source of immune 1,25D are still to be determined.

Crucially, the expression of *CYP27B1* has also been described in T cells (57). To date, the relevance of this for T cell synthesis of 1,25D has been unclear but recent studies by Chauss *et al*. have shown that C3b Complement activation of human T cells via CD46 induced *VDR* and *CYP27B1* expression in the resulting Th1 cells (58). Here, both 25D and 1,25D were able to regulate expression of key genes associated with Th1 cell function, such as IFNγ and IL-17, demonstrating a functional intracrine pathway for 25D/1,25D in T cells (58). In this particular study, the authors have hypothesised that intracrine metabolism could provide a basis for the reported link between low serum 25D and severity of Th1 cell inflammation in patients with COVID-19 disease. However, as outlined in Fig. 2, it is also possible to speculate that similar dysregulation of intracrine 1,25D and Th1 cell function may contribute to the development and severity of the autoimmune disease.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

Synthesis of and response to 1,25D with inflammation

The dynamics of the intracrine vs paracrine effects of 1,25D on T cell function remain unclear, particularly as T cells are themselves able to stimulate DC expression of *CYP27B1* when in contact with DC (47). It is possible that both intracrine and paracrine actions of 1,25D occur *in vivo*, but the magnitude of influence of each pathway may depend on the local availability of 25D for metabolism. Specifically, lower concentrations of 25D may be adequate to drive the intracrine effects on DC antigen presentation, but not sufficient to enable secretion of enough 1,25D to influence T cells in a paracrine fashion. Conversely, conditions of 25D repletion may act to enhance both intracrine and paracrine responses to DC-synthesised 1,25D. Paracrine release of 1,25D may also provide a mechanism by which DC are able to support the initial activation of T cells while moderating over-exuberant inflammation. Specifically, there appears to be a reciprocal relationship between expression of 1α-hydroxylase and VDR as DC differentiate, with mature DC having higher levels of 1α-hydroxylase but lower VDR than immature DC (31). Thus, it is possible that for mature DC the intracrine pathway is limited by lower levels of VDR, while paracrine actions on neighbouring immature DC may be more viable as these cells express more VDR (59). In this way, paracrine 1,25D would favour the maturation of some DCs to prime T cell activation, while inhibiting the further development of other less mature DCs to prevent an exponential increase in T cell activation. Another potential benefit of combined intracrine and paracrine actions of 1,25D during antigen presentation is to better facilitate the development of memory T cells. Inflammatory stimuli are required to activate DC to enable antigen presentation and subsequent expansion of effector T cells and the development of memory T cell pools. However, sustained inflammation impairs the effective generation of memory T cells via inappropriately sustained T cell proliferation and apoptosis (60). In this setting, intracrine 1,25D may act to moderate DC maturation and antigen presentation, while paracrine 1,25D may attenuate the inflammatory environment during effector T cell development. Collectively, this would then favour the development of more tolerogenic T cell responses with enhanced memory T cell development.

Vitamin D metabolism and function in autoimmune disease

The majority of reports linking 1,25D with immune function have involved studies of normal peripheral blood cells cultured under inflammatory conditions *in vitro*. However, the effects of 1,25D may be more complex in the setting of inflammatory disease. In studies using synovial fluid, we showed that T cells from the inflamed joints of rheumatoid arthritis (RA) patients are insensitive to the anti-inflammatory effects of 1,25D relative to paired blood T cells from the same patient, despite expressing similar levels of VDR (61). This T cell 'resistance' to 1,25D was due in part to the predominant memory T cell phenotype in RA joint synovial fluid. However, other, tissue-specific, mechanisms are also involved as memory T cells from RA synovial fluid were less sensitive to 1,25D than circulating memory T cells from the same patient (61). Collectively these observations indicate that some of the T cell anti-inflammatory/tolerogenic effects of 1,25D on T cells observed *in vitro* may be less effective *in vivo* in the setting of inflammatory disease. Specifically, the ability of T cells to respond to 1,25D in an inflammatory disease setting correlated inversely with the capacity of phenotype change in the T cells – the more committed cells are phenotypically, the less responsive they are to 1,25D. The precise mechanism for this remains unclear but does not appear to be due to impaired capacity for 1,25D signalling.

As outlined earlier, a key observation linking vitamin D with the immune system is the capacity for synthesis of 1,25D by macrophages from patients with sarcoidosis, with this extra-renal 1α-hydroxylase activity being sufficient to raise circulating levels of 1,25D in some patients (20). Elevated serum levels of 1,25D have also been reported for patients with some autoimmune disorders. In patients with Crohn's disease, but not ulcerative colitis, raised serum 1,25D has been associated with decreased bone mineral density, although the precise source of increased 1,25D in these inflammatory bowel disease (IBD) patients remains unclear (62). By contrast, in patients with RA, macrophages from the synovial fluid exhibit increased capacity for synthesis of 1,25D relative to macrophages from patients with osteoarthritis (63). However, this potential for enhanced macrophage 1,25D production in RA may also lead to elevated serum levels of 1,25D (64), although this appears to be dependent on the availability of 25D in the RA patients (65). In a recent analysis of multiple vitamin D metabolites from patients with RA, serum 1,25D levels were not statistically different from healthy controls, and were higher than paired synovial fluid 1,25D concentrations from the same patients (66). Despite the apparent lack of elevated 1,25D in RA patients in the absence of vitamin D supplementation, both serum 25D and 1,25D levels have been reported to

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

show inverse correlation with RA disease activity scores, suggesting that increased synovial inflammation is not driving systemic spill-over of any immune cell-derived 1,25D (67). In other autoimmune disorders such as MS, serum 1,25D concentrations do not appear to be higher in patients vs controls (68), and have been reported to decline with MS relapse rate (69). In both cases, the circulating levels of 1,25D in patients with MS appear to be highly dependent on serum 25D concentrations and do not appear to be driven by inflammatory disease activity. The over-arching conclusion from these observations is that while extra-renal metabolism of 25D to 1,25D is a key feature of autoimmune disorders, this does not appear to be associated with the unregulated 1α-hydroxylase activity that is characteristic of granulomatous diseases.

Vitamin D-deficiency, genetic variation in the vitamin D system and animal models of autoimmune disease

Low serum concentrations of 25D are a common health issue across the globe (70, 71). While this continues to provide a challenge to calcium homeostasis and bone

Table 1 Summary of reported studies of vitamin D and specific autoimmune disease. Publications for individual autoimmune diseases reporting effects of (i) serum vitamin D-deficiency; (ii) genetic variation in vitamin D status determined by Mendelian randomisation; (iii) SNPs for specific components of the vitamin D transport/metabolism/signalling system.

Autoimmune disorder	Vitamin D deficiency	Mendelian randomisation	SNPs
Rheumatoid arthritis	Reviewed in Harrison *et al.* 2020 (49)	Bae and Lee 2018 (83) Viatte *et al.* 2014 (84)	*VDR* systematic review Bagheri-Hosseinabadi *et al.* 2020 (85) *DBP/GC* Yan *et al.* 2012 (86)
Sjögren's syndrome	Systematic review Kuo *et al.* 2020 (87) Li *et al.* 2019 (88) Erten *et al.* 2015 (89)		
Systemic lupus erythematosus	Arshad *et al.* 2021 (90) Reviewed in Kamen *et al.* 2006 (91) Reviewed in Dall'Ara *et al.* 2018 (92)	Bae and Lee 2018 (83)	*VDR* Chen *et al.* 2017 (93) *CYP27B1* Fakhfakh *et al.* 2021 (94)
Inflammatory bowel disease (IBD)	Systematic Review Del Pinto *et al.* 2015 (95) Systematic Review Gubatan *et al.* 2019 (96)	Lund-Nielsen *et al.* 2018 (97)	*VDR* Gisbert-Ferrándiz *et al.* 2018 (98) *DBP/GC* Eloranta *et al.* 2011 (99)
Multiple sclerosis (MS)	Reviewed in Sintzel *et al.* 2018 (100)	Mokry *et al.* 2015 (78) Rhead *et al.* 2016 (79) Harroud *et al.* 2018 (101)	*CYP27B1* Sundqvist *et al.* 2010 (102); Orton *et al.* 2008 (103) *CYP2R1* Scazzone *et al.* 2018 (104) *DBP/GC* Agliardi *et al.* 2017 (105) *VDR* Reviewed in Scazzone *et al.* 2021(106)
Type 1 diabetes mellitus	Meta-analysis Hou *et al.* 2021 (107) Meta-analysis Feng *et al.* 2015 (108)	Manousaki *et al.* 2021 (109)	*VDR* Nejentsev *et al.* 2004 (110) *CYP2R1, DBP/GC, CYP24A1* Almeida *et al.* 2020 (111)
Guillain-Barre syndrome	Elf *et al.* 2014 (112)		
Chronic inflammatory demyelinating polyneuropathy			
Psoriasis	Fu *et al.* 2021 (113) Pitukweerakul *et al.* 2019 (114) Reviewed in Hambly and Kirby 2017 (115)		*VDR* Liu *et al.* 2020 (116)
Autoimmune thyroid disease	Ke *et al.* 2017 (117) Xu *et al.* 2015 (118) Wang *et al.* 2015 (119)		*VDR* Zhou *et al.* 2021 (120) *VDR* Meng *et al.* 2015 (121) *CYP27B1* Jennings *et al.* 2005 (122)
Myasthenia gravis	Justo *et al.* 2021 (123) Kang *et al.* 2018 (124) Askmark *et al.* 2012 (125)		*VDR* Han *et al.* 2021 (126)
Vasculitis	Korkmaz *et al.* 2021 (127) Yoon *et al.* 2020 (128) Systematic Review Khabbazi *et al.* (2019) (129)	Zhong *et al.* 2021 (130)	

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

health in both adults and children (72, 73), there has also been a dramatic increase in studies reporting extra-skeletal health issues in the setting of 25D-deficiency (74). Prominent amongst these are association studies linking low serum 25D status with immune dysregulation, notably autoimmune disease. Table 1 summarises the various reports that have assessed the impact of 25D status on specific autoimmune diseases. The central conclusion from these studies is that low serum 25D concentrations are associated with increased prevalence and/or severity of autoimmune disease, but the key question remains as to whether 25D-deficiency is a cause or consequence of autoimmune disease. To address this question, more recent studies have assessed the impact of genetic variability within the vitamin D system as a marker of lifelong variations in 25D status. One approach to this has been to determine if SNPs in genes associated with vitamin D metabolism, transport or function correlate with the prevalence or severity of autoimmune diseases. These genes primarily include serum DBP (*GC*), 25-hydroxylase (*CYP2R1*), *CYP27B1*, 24-hydroxylase (*CYP24A1*) and *VDR*. The general conclusion from these studies is that genetic variations within the vitamin D system, notably *VDR*, may contribute to autoimmune disease susceptibility. The major caveat is that the functional relevance of many of these SNPs is still unclear and, thus, the impact of this genetic variability cannot yet be fully defined.

Some vitamin D-related SNPs, notably *GC* and *CYP2R1*, have been linked to serum 25D concentrations (75). The correlation between vitamin D SNPs and serum 25D levels means that it is possible to predict gene haplotypes that are associated with higher vs lower serum 25D status over the lifetime of a particular individual. The prevalence of these SNPs in patient cohorts therefore has the potential to provide a statistically robust analysis of whether particular SNPs linked to low serum 25D are more common in a specific disease, a process known as Mendelian randomization (MR) (76). The advantages of this strategy are that it enables the analysis of large numbers of subjects and provides a long-term perspective of serum 25D status that is independent of potential confounders and disease influence. The disadvantages of MR are that the genetic variations used in this analysis are only a small component of the overall serum level of 25D, with one study estimating this to be approximately 7.5% (77). The other key caveat with MR is that this analysis of the genetic component of 25D status is less accurate at sub-optimal serum concentrations of 25D. Thus, in populations, including the UK, where serum 25D levels are known to be persistently low, particularly in winter months, MR analysis of vitamin D-related SNPs may have limited value. Nevertheless, MR strategy has been used to investigate further the links between serum 25D levels and specific autoimmune diseases (see Table 1). Broadly speaking, data do not support a significant association between genetically defined 25D levels and autoimmune disease. The notable exception to this is MS, where studies have reported significant associations for this disease (78, 79). This, coupled with the association between low serum 25D and MS, and the links between MS and several individual vitamin D system SNPs, means that of all the autoimmune diseases, MS has the strongest link to vitamin D.

Vitamin D and autoimmune disease in animal models

In addition to studies of serum 25D status and genetic variations in humans, the associations between vitamin D and autoimmune disease have been explored using animal models, predominantly mice. This includes the analysis of mice under conditions of 25D deficiency, and or following supplementation with vitamin D or 1,25D, and the use of mice with knockout or transgenic expression of genes from the vitamin D system. A summary of key publications from these animal studies is shown in Table 2. Consistent with human studies, 25D-deficient mice appear to be more susceptible to mouse models of specific autoimmune diseases. In contrast to human studies, vitamin D supplementation in mouse models of autoimmune disease has to date primarily involved treatment with 1,25D rather than conventional vitamin D supplementation used for human studies. In most cases this strategy ameliorated the specific disease, suggesting that elevated circulating 1,25D is sufficient to modulate inflammatory disease in animal models. This raises the question of whether the intracrine 25D metabolism model that has arisen from studies of human immune cells *in vitro* is generalisable to animal models *in vivo*. It is also important to recognise that potential hypercalcemic effects of 1,25D maybe less evident in mouse models of inflammatory disease, and the long-term efficacy of similar strategies in humans is far from clear and may be clinically unacceptable because of the potential hypercalcemic side-effects of 1,25D. In a similar fashion to 25D-deficiency, murine knockout of vitamin D genes such *Vdr* and *Cyp27b1* appears to exacerbate mouse versions of all of the autoimmune diseases studied so far, suggesting that the vitamin D system plays some part in moderating the immune responses that are associated with the inflammatory disease in these mouse models.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

Table 2 Mouse models of vitamin D and specific autoimmune disease. Publications for individual autoimmune diseases reporting effects of (i) dietary vitamin D-deficiency; (ii) supplementation with vitamin D or 1,25-dihydroxyvitamin D (1,25D); (iii) knockout/over-expression of specific vitamin D-related genes.

Autoimmune disorder	Vitamin D deficiency	Vitamin D supplementation	Gene knockout/transgene
Rheumatoid arthritis		1,25D Cantorna *et al*. 1998 (131) 1,25D Zhou *et al*. 2019 (132) 1,25D Galea *et al*. 2019 (133)	*Vdr* Zwerina *et al*. 2011 (134) *Cyp27b1* Gu *et al*. 2016 (135)
Systemic lupus erythematosus	Reynolds *et al*. 2016 (136) Yamamoto *et al*. 2020 (137)	Vitamin D Correa Freitas *et al*. 2019 (138)	
Inflammatory bowel disease	Lagishetty *et al*. 2010 (139) Assa *et al*. 2014 (140) Ryz *et al*. 2015 (141) Wei *et al*. 2021 (142)	1,25D analogue Laverny *et al*. 2010 (143) 1,25D Ooi *et al*. 2013 (144) Vitamin D Yoo *et al*. 2019 (145)	*Vdr* Froicu *et al*. 2003 (146) *Vdr* Kong *et al*. 2007 (147) *Cyp27b1* Liu *et al*. (148) *Vdr* Kim *et al*. 2013 (149) *Vdr* Lu *et al*. 2021 (150)
Multiple sclerosis	DeLuca and Plum 2011 (151) Wang *et al*. 2012 (152) Fernandes de Abreu *et al*. 2012 (153)	1,25D Cantorna *et al*. 1996 (154) 1,25D Spach *et al*. 2004 (155) 1,25D Spach *et al*. 2006 (156) 1,25D Mayne *et al*. 2011 (157)	*Vdr* Wang *et al*. 2012 (152) *Cyp27b1* Wang *et al*. 2016 (158)
Type 1 diabetes mellitus	Giulietti *et al*. 2004 (159) Mathieu *et al*. 2004 (160)	1,25D Zella *et al*. 2003 (161)	*Vdr* Mathieu *et al*. 2001 (162) *Vdr* Gysemans *et al*. 2008 (163) *Vdr* Morro *et al*. 2020 (164) *Gc* Viloria *et al*. 2021 (165)
Psoriasis			*Vdr* Kong *et al*. 2006 (166)
Autoimmune thyroid disease	Misharin *et al*. 2009 (167)		
Vasculitis		1,25D Choi *et al*. 2011 (168) 1,25D Galea *et al*. 2019 (133)	

Conclusions and future challenges

The aim of this review is to provide a mechanistic and model context for the interconnection between vitamin D and autoimmune disease. The general conclusion from the studies described in this review is that there is an association between low serum levels of 25D and autoimmunity. Supporting this statement are robust data that 1,25D has potent immunomodulatory effects on leukocytes, consistent associations between 25D-deficiency in humans and animals, autoimmune disease prevalence and severity and beneficial effects of vitamin D supplementation in animal models. To date, the crucial missing piece of the jigsaw has been the absence of robust randomised controlled trials of vitamin D supplementation in humans. This is a subject in its own right and has not been discussed in detail in the current review. Nevertheless, it is important to highlight recent randomised control trial data from the Vitamin D and Omega 3 Trial involving 25,871 participants supplemented with placebo, omega 3 fatty acids or vitamin D (2000 IU/day). Supplementation with vitamin D, with or without omega 3 fatty acids, was shown to decrease the incidence of autoimmune disease in this cohort by 22% after a follow-up of 5 years (with a 39% reduction when only the last 3 years of the study were considered) (80). It is therefore clear that successful use of vitamin D to prevent autoimmune disease is possible but may require lengthy periods of supplementation.

Another key challenge in designing effective supplementation trials to assess the potential impact of vitamin D on autoimmune disease is that it is still not clear what serum level of 25D is optimal for immune function. It is possible that the target level for serum 25D is different from more generalised recommendations made by organisations such as the Institute of Medicine that are based on bone health (81). It is also possible that different levels of 25D are optimal for innate antibacterial and antiviral responses relative to anti-inflammatory effects. Another important consideration is whether vitamin D can be used to help prevent autoimmune disease or whether it provides any therapeutic benefit once the disease has become established. Again, it is quite likely that these two different facets of vitamin D treatment will require different serum levels of 25D for optimal function.

It is also important to recognise that almost all studies of vitamin D supplementation and human disease outcomes have relied on a single marker to define vitamin D deficiency or – sufficiency – namely serum concentrations of 25D. Serum 25D is a relatively cheap and straightforward measurement but this neglects the fact that 25D is an inactive form of vitamin. Recent studies have demonstrated that, like other steroid hormones, vitamin D

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0554

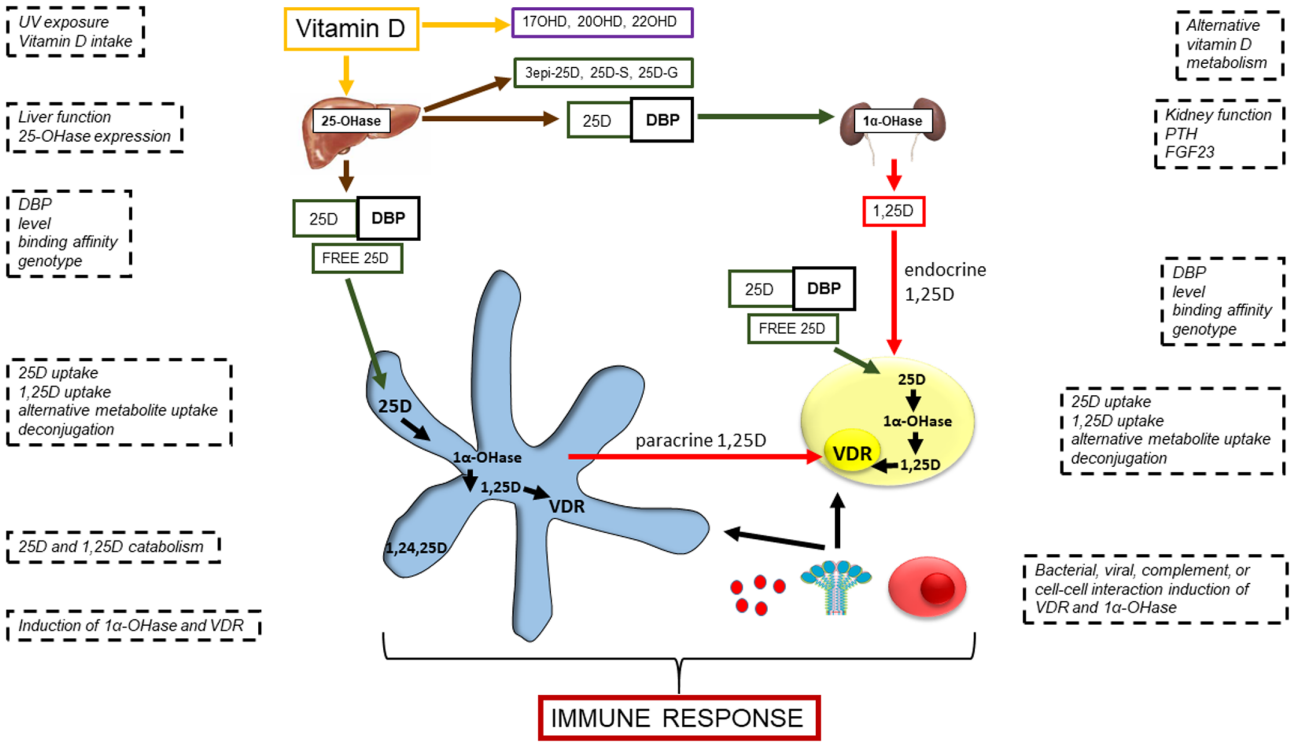

Figure 3

Determinants of the impact of vitamin D on immune function. Schematic showing the diverse array of mechanisms that can influence the interaction between vitamin D and the immune system. The principal marker of vitamin D function continues to be serum levels of 25-hydroxyvitamin D (25D) as determined by exposure to UV light or dietary intake of vitamin D and liver activity of the enzyme 25-hydroxylase (25-OHase). However, vitamin D is also converted to alternative metabolites by the cholesterol side-chain cleavage enzyme. 25D can also circulate as epi or conjugated forms. Transport of vitamin D metabolites, particularly 25D, involves the vitamin D binding protein (DBP) which is essential for renal conversion of 25D to 1,25-dihydroxvitamin D (1,25D) by 1α-hydroxylase (1α-OHase). By contrast, acquisition of 25D by immune cells appears to involve free (unbound) 25D and subsequent 1α-OHase activity. In immune cells, the level of 1α-OHase expression, as well as expression of the vitamin D receptor (VDR) for 1,25D may be defined by various regulators of immune cell function including bacteria, viruses, complement and other immune cells. Collectively, these factors, along with catabolic activity of enzymes such as 24-hydroxylase act to enhance or attenuate the central effects of serum 25D in driving innate and adaptive immune responses. Text boxes on each side (dashed lines) describe the different mechanisms that modify the core effects of altered serum 25D levels.

is defined by a wide range of metabolites that constitute the 'vitamin D metabolome', including active 1,25D (1) (see Fig. 1). Other, less commonly measured, vitamin D metabolites may also have distinct immunomodulatory actions in their own right. For example, recent studies have shown that the cholesterol side-chain cleavage enzyme can metabolise vitamin D before conversion to 25D (3). One of the metabolites from this enzyme activity, 20S-hydroxyvitamin D, has potent anti-inflammatory effects that do not require metabolism by CYP27B1 (82). This coupled with the distinct mechanisms for the uptake and catabolism of 25D and 1,25D, as well as the presence of reservoirs of conjugated and epi forms of 25D outlined in Fig. 1, means that relatively simplistic model for intracrine immune modulation initially proposed for 25D is now outmoded. In the original model, it was proposed that simple changes in serum 25D levels were sufficient to define extra-skeletal functions of vitamin D such as its effects on anti-inflammatory immunity. We can now greatly expand this model to include not only the concentration of 25D but also its transport, and target cell levels of 1α-hydroxylase and VDR, as well as the catabolic enzymes that attenuate 25D/1,25D function (Fig. 3). Thus, it will be important in future studies to broaden our perspectives beyond simple serum measurement of 25D to include multiple other vitamin D metabolites and possibly genetic variants for proteins in the vitamin D system.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

J F is funded by the National Institute for Health Research (NIHR) and Health Education England through a Clinical Doctoral Research Fellowship, ICA-CDRF-2017-03-083. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

and Social Care. E L B is supported by a MIDAS PhD studentship from the Wellcome Trust. K R is supported by the NIHR Birmingham Biomedical Research Centre.

References

1 Jenkinson C. The vitamin D metabolome: an update on analysis and function. *Cell Biochemistry and Function* 2019 **37** 408–423. (https://doi.org/10.1002/cbf.3421)

2 Jenkinson C, Desai R, McLeod MD, Wolf Mueller J, Hewison M & Handelsman DJ. Circulating conjugated and unconjugated vitamin D metabolite measurements by liquid chromatography mass spectrometry. *Journal of Clinical Endocrinology and Metabolism* 2022 **107** 435–449. (https://doi.org/10.1210/clinem/dgab708)

3 Slominski AT, Kim TK, Shehabi HZ, Semak I, Tang EK, Nguyen MN, Benson HA, Korik E, Janjetovic Z, Chen J, *et al.* In vivo evidence for a novel pathway of vitamin D(3) metabolism initiated by P450scc and modified by CYP27B1. *FASEB Journal* 2012 **26** 3901–3915. (https://doi.org/10.1096/fj.12-208975)

4 Pike JW, Lee SM, Benkusky NA & Meyer MB. Genomic mechanisms governing mineral homeostasis and the regulation and maintenance of vitamin D metabolism. *JBMR Plus* 2021 **5** e10433. (https://doi.org/10.1002/jbm4.10433)

5 Carlberg C. Nutrigenomics of vitamin D. *Nutrients* 2019 **11** 676. (https://doi.org/10.3390/nu11030676)

6 Haussler MR, Whitfield GK, Kaneko I, Forster R, Saini R, Hsieh JC, Haussler CA & Jurutka PW. The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis. *Reviews in Endocrine and Metabolic Disorders* 2012 **13** 57–69. (https://doi.org/10.1007/s11154-011-9199-8)

7 Chun RF, Peercy BE, Orwoll ES, Nielson CM, Adams JS & Hewison M. Vitamin D and DBP: the free hormone hypothesis revisited. *Journal of Steroid Biochemistry and Molecular Biology* 2014 **144** 132–137. (https://doi.org/10.1016/j.jsbmb.2013.09.012)

8 Hypponen E & Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *American Journal of Clinical Nutrition* 2007 **85** 860–868. (https://doi.org/10.1093/ajcn/85.3.860)

9 Scientific Advisory Committee on Nutrition (SACN). *SACN Vitamin D and Health Report*. Public Health England, 2016. (available at: https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report)

10 Adams JS & Hewison M. Update in vitamin D. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 471–478. (https://doi.org/10.1210/jc.2009-1773)

11 Hong Q, Xu J, Xu S, Lian L, Zhang M & Ding C. Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis. *Rheumatology* 2014 **53** 1994–2001. (https://doi.org/10.1093/rheumatology/keu173)

12 Park YE, Kim BH, Lee SG, Park EK, Park JH, Lee SH & Kim GT. Vitamin D status of patients with early inflammatory arthritis. *Clinical Rheumatology* 2015 **34** 239–246. (https://doi.org/10.1007/s10067-014-2613-3)

13 Di Franco M, Barchetta I, Iannuccelli C, Gerardi MC, Frisenda S, Ceccarelli F, Valesini G & Cavallo MG. Hypovitaminosis D in recent onset rheumatoid arthritis is predictive of reduced response to treatment and increased disease activity: a 12 month follow-up study. *BMC Musculoskeletal Disorders* 2015 **16** 53. (https://doi.org/10.1186/s12891-015-0505-6)

14 Hewison M. Vitamin D and immune function: an overview. *Proceedings of the Nutrition Society* 2012 **71** 50–61. (https://doi.org/10.1017/S0029665111001650)

15 Hewison M. Vitamin D and innate and adaptive immunity. *Vitamins and Hormones* 2011 **86** 23–62. (https://doi.org/10.1016/B978-0-12-386960-9.00002-2)

16 Adams JS & Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nature Clinical Practice: Endocrinology and Metabolism* 2008 **4** 80–90. (https://doi.org/10.1038/ncpendmet0716)

17 Jeffery LE, Raza K & Hewison M. Vitamin D in rheumatoid arthritis-towards clinical application. *Nature Reviews: Rheumatology* 2016 **12** 201–210. (https://doi.org/10.1038/nrrheum.2015.140)

18 Provvedini DM, Tsoukas CD, Deftos LJ & Manolagas SC. 1,25-Dihydroxyvitamin D3 receptors in human leukocytes. *Science* 1983 **221** 1181–1183. (https://doi.org/10.1126/science.6310748)

19 Veldman CM, Cantorna MT & DeLuca HF. Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Archives of Biochemistry and Biophysics* 2000 **374** 334–338. (https://doi.org/10.1006/abbi.1999.1605)

20 Adams JS, Sharma OP, Gacad MA & Singer FR. Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. *Journal of Clinical Investigation* 1983 **72** 1856–1860. (https://doi.org/10.1172/JCI111147)

21 Kallas M, Green F, Hewison M, White C & Kline G. Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 3111–3117. (https://doi.org/10.1210/jc.2009-2673)

22 Kreutz M, Andreesen R, Krause SW, Szabo A, Ritz E & Reichel H. 1,25-Dihydroxyvitamin D3 production and vitamin D3 receptor expression are developmentally regulated during differentiation of human monocytes into macrophages. *Blood* 1993 **82** 1300–1307.

23 Teles RM, Graeber TG, Krutzik SR, Montoya D, Schenk M, Lee DJ, Komisopoulou E, Kelly-Scumpia K, Chun R, Iyer SS, *et al.* Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. *Science* 2013 **339** 1448–1453. (https://doi.org/10.1126/science.1233665)

24 Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, *et al.* Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006 **311** 1770–1773. (https://doi.org/10.1126/science.1123933)

25 Hewison M. Antibacterial effects of vitamin D. *Nature Reviews: Endocrinology* 2011 **7** 337–345. (https://doi.org/10.1038/nrendo.2010.226)

26 Gal-Tanamy M, Bachmetov L, Ravid A, Koren R, Erman A, Tur-Kaspa R & Zemel R. Vitamin D: an innate antiviral agent suppressing hepatitis C virus in human hepatocytes. *Hepatology* 2011 **54** 1570–1579. (https://doi.org/10.1002/hep.24575)

27 Kalia V, Studzinski GP & Sarkar S. Role of vitamin D in regulating COVID-19 severity-an immunological perspective. *Journal of Leukocyte Biology* 2021 **110** 809–819. (https://doi.org/10.1002/JLB.4COVR1020-698R)

28 Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR & Tangpricha V. Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. *Journal of Translational Medicine* 2009 **7** 28. (https://doi.org/10.1186/1479-5876-7-28)

29 Jolliffe DA, Camargo Jr CA, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, Bergman P, Bischoff-Ferrari HA, Borzutzky A, Damsgaard CT, *et al.* Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet: Diabetes and Endocrinology* 2021 **9** 276–292. (https://doi.org/10.1016/S2213-8587(21)00051-6)

30 Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, Madhavan MV, Nair N, Babalyan V, Hutchings N, *et al.* MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19. *European Journal of Endocrinology* 2020 **183** R133–R147. (https://doi.org/10.1530/EJE-20-0665)

31 Hewison M, Freeman L, Hughes SV, Evans KN, Bland R, Eliopoulos AG, Kilby MD, Moss PA & Chakraverty R. Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells.

Journal of Immunology 2003 **170** 5382–5390. (https://doi.org/10.4049/jimmunol.170.11.5382)

32 Fritsche J, Mondal K, Ehrnsperger A, Andreesen R & Kreutz M. Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. *Blood* 2003 **102** 3314–3316. (https://doi.org/10.1182/blood-2002-11-3521)

33 Brennan A, Katz DR, Nunn JD, Barker S, Hewison M, Fraher LJ & O'Riordan JL. Dendritic cells from human tissues express receptors for the immunoregulatory vitamin D3 metabolite, dihydroxycholecalciferol. *Immunology* 1987 **61** 457–461.

34 Griffin MD, Lutz WH, Phan VA, Bachman LA, McKean DJ & Kumar R. Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs. *Biochemical and Biophysical Research Communications* 2000 **270** 701–708. (https://doi.org/10.1006/bbrc.2000.2490)

35 Penna G & Adorini L. 1Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *Journal of Immunology* 2000 **164** 2405–2411. (https://doi.org/10.4049/jimmunol.164.5.2405)

36 Adorini L, Penna G, Giarratana N & Uskokovic M. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting allograft rejection and autoimmune diseases. *Journal of Cellular Biochemistry* 2003 **88** 227–233. (https://doi.org/10.1002/jcb.10340)

37 Adorini L. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting autoimmune diabetes. *Annals of the New York Academy of Sciences* 2003 **987** 258–261. (https://doi.org/10.1111/j.1749-6632.2003.tb06057.x)

38 Penna G, Amuchastegui S, Giarratana N, Daniel KC, Vulcano M, Sozzani S & Adorini L. 1,25-Dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. *Journal of Immunology* 2007 **178** 145–153. (https://doi.org/10.4049/jimmunol.178.1.145)

39 Penna G, Roncari A, Amuchastegui S, Daniel KC, Berti E, Colonna M & Adorini L. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. *Blood* 2005 **106** 3490–3497. (https://doi.org/10.1182/blood-2005-05-2044)

40 Pedersen AW, Holmstrom K, Jensen SS, Fuchs D, Rasmussen S, Kvistborg P, Claesson MH & Zocca MB. Phenotypic and functional markers for 1alpha,25-dihydroxyvitamin D(3)-modified regulatory dendritic cells. *Clinical and Experimental Immunology* 2009 **157** 48–59. (https://doi.org/10.1111/j.1365-2249.2009.03961.x)

41 Szeles L, Keresztes G, Torocsik D, Balajthy Z, Krenacs L, Poliska S, Steinmeyer A, Zuegel U, Pruenster M, Rot A, *et al.* 1,25-Dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. *Journal of Immunology* 2009 **182** 2074–2083. (https://doi.org/10.4049/jimmunol.0803345)

42 Griffin MD, Xing N & Kumar R. Gene expression profiles in dendritic cells conditioned by 1alpha,25-dihydroxyvitamin D3 analog. *Journal of Steroid Biochemistry and Molecular Biology* 2004 89–90 443–448.

43 Ferreira GB, van Etten E, Lage K, Hansen DA, Moreau Y, Workman CT, Waer M, Verstuyf A, Waelkens E, Overbergh L, *et al.* Proteome analysis demonstrates profound alterations in human dendritic cell nature by TX527, an analogue of vitamin D. *Proteomics* 2009 **9** 3752–3764. (https://doi.org/10.1002/pmic.200800848)

44 Ferreira GB, Vanherwegen AS, Eelen G, Gutierrez ACF, Van Lommel L, Marchal K, Verlinden L, Verstuyf A, Nogueira T, Georgiadou M, *et al.* Vitamin D3 induces tolerance in human dendritic cells by activation of intracellular metabolic pathways. *Cell Reports* 2015 **10** 711–725. (https://doi.org/10.1016/j.celrep.2015.01.013)

45 Munoz Garcia A, Kutmon M, Eijssen L, Hewison M, Evelo CT & Coort SL. Pathway analysis of transcriptomic data shows immunometabolic effects of vitamin D. *Journal of Molecular Endocrinology* 2018 **60** 95–108. (https://doi.org/10.1530/JME-17-0186)

46 Garcia AM, Bishop EL, Li D, Jeffery LE, Garten A, Thakker A, Certo M, Mauro C, Tennant DA, Dimeloe S, *et al.* Tolerogenic effects of 1,25-dihydroxyvitamin D on dendritic cells involve induction of fatty acid synthesis. *Journal of Steroid Biochemistry and Molecular Biology* 2021 **211** 105891. (https://doi.org/10.1016/j.jsbmb.2021.105891)

47 Jeffery LE, Wood AM, Qureshi OS, Hou TZ, Gardner D, Briggs Z, Kaur S, Raza K & Sansom DM. Availability of 25-hydroxyvitamin D3 to APCs controls the balance between regulatory and inflammatory T cell responses. *Journal of Immunology* 2012 **189** 5155–5164. (https://doi.org/10.4049/jimmunol.1200786)

48 Cantorna MT. Vitamin D, multiple sclerosis and inflammatory bowel disease. *Archives of Biochemistry and Biophysics* 2012 **523** 103–106. (https://doi.org/10.1016/j.abb.2011.11.001)

49 Harrison SR, Li D, Jeffery LE, Raza K & Hewison M. Vitamin D, autoimmune disease and rheumatoid arthritis. *Calcified Tissue International* 2020 **106** 58–75. (https://doi.org/10.1007/s00223-019-00577-2)

50 Chun RF, Lauridsen AL, Suon L, Zella LA, Pike JW, Modlin RL, Martineau AR, Wilkinson RJ, Adams J & Hewison M. Vitamin D-binding protein directs monocyte responses to 25-hydroxy- and 1,25-dihydroxyvitamin D. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 3368–3376. (https://doi.org/10.1210/jc.2010-0195)

51 Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, Walker LS, Lammas DA, Raza K & Sansom DM. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *Journal of Immunology* 2009 **183** 5458–5467. (https://doi.org/10.4049/jimmunol.0803217)

52 Provvedini DM & Manolagas SC. 1Alpha,25-dihydroxyvitamin D3 receptor distribution and effects in subpopulations of normal human T lymphocytes. *Journal of Clinical Endocrinology and Metabolism* 1989 **68** 774–779. (https://doi.org/10.1210/jcem-68-4-774)

53 Sarkar S, Hewison M, Studzinski GP, Li YC & Kalia V. Role of vitamin D in cytotoxic T lymphocyte immunity to pathogens and cancer. *Critical Reviews in Clinical Laboratory Sciences* 2016 **53** 132–145. (https://doi.org/10.3109/10408363.2015.1094443)

54 Meehan TF & DeLuca HF. CD8(+) T cells are not necessary for 1 alpha,25-dihydroxyvitamin D(3) to suppress experimental autoimmune encephalomyelitis in mice. *PNAS* 2002 **99** 5557–5560. (https://doi.org/10.1073/pnas.082100699)

55 Ooi JH, McDaniel KL, Weaver V & Cantorna MT. Murine CD8+ T cells but not macrophages express the vitamin D 1alpha-hydroxylase. *Journal of Nutritional Biochemistry* 2014 **25** 58–65. (https://doi.org/10.1016/j.jnutbio.2013.09.003)

56 Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D & Butcher EC. DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. *Nature Immunology* 2007 **8** 285–293. (https://doi.org/10.1038/ni1433)

57 Smolders J, Thewissen M, Theunissen R, Peelen E, Knippenberg S, Menheere P, Cohen Tervaert JW, Hupperts R & Damoiseaux J. Vitamin D-related gene expression profiles in immune cells of patients with relapsing remitting multiple sclerosis. *Journal of Neuroimmunology* 2011 **235** 91–97. (https://doi.org/10.1016/j.jneuroim.2011.03.012)

58 Chauss D, Freiwald T, McGregor R, Yan B, Wang L, Nova-Lamperti E, Kumar D, Zhang Z, Teague H, West EE, *et al.* Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. *Nature Immunology* 2022 **23** 62–74. (https://doi.org/10.1038/s41590-021-01080-3)

59 Hewison M, Zehnder D, Chakraverty R & Adams JS. Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. *Molecular and Cellular Endocrinology* 2004 **215** 31–38. (https://doi.org/10.1016/j.mce.2003.11.017)

60 Woodland DL & Blackman MA. Vaccine development: baring the 'dirty little secret'. *Nature Medicine* 2005 **11** 715–716. (https://doi.org/10.1038/nm0705-715)

61 Jeffery LE, Henley P, Marium N, Filer A, Sansom DM, Hewison M & Raza K. Decreased sensitivity to 1,25-dihydroxyvitamin D3 in T cells from the rheumatoid joint. *Journal of Autoimmunity* 2018 **88** 50–60. (https://doi.org/10.1016/j.jaut.2017.10.001)

62 Abreu MT, Kantorovich V, Vasiliauskas EA, Gruntmanis U, Matuk R, Daigle K, Chen S, Zehnder D, Lin YC, Yang H, *et al.* Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density. *Gut* 2004 **53** 1129–1136. (https://doi.org/10.1136/gut.2003.036657)

63 Hayes ME, Denton J, Freemont AJ & Mawer EB. Synthesis of the active metabolite of vitamin D, 1,25(OH)2D3, by synovial fluid macrophages in arthritic diseases. *Annals of the Rheumatic Diseases* 1989 **48** 723–729. (https://doi.org/10.1136/ard.48.9.723)

64 Gates S, Shary J, Turner RT, Wallach S & Bell NH. Abnormal calcium metabolism caused by increased circulating 1,25-dihydroxyvitamin D in a patient with rheumatoid arthritis. *Journal of Bone and Mineral Research* 1986 **1** 221–226. (https://doi.org/10.1002/jbmr.5650010209)

65 Mawer EB, Hayes ME, Still PE, Davies M, Lumb GA, Palit J & Holt PJ. Evidence for nonrenal synthesis of 1,25-dihydroxyvitamin D in patients with inflammatory arthritis. *Journal of Bone and Mineral Research* 1991 **6** 733–739. (https://doi.org/10.1002/jbmr.5650060711)

66 Li D, Jeffery LE, Jenkinson C, Harrison SR, Chun RF, Adams JS, Raza K & Hewison M. Serum and synovial fluid vitamin D metabolites and rheumatoid arthritis. *Journal of Steroid Biochemistry and Molecular Biology* 2019 **187** 1–8. (https://doi.org/10.1016/j.jsbmb.2018.10.008)

67 Patel S, Farragher T, Berry J, Bunn D, Silman A & Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. *Arthritis and Rheumatism* 2007 **56** 2143–2149. (https://doi.org/10.1002/art.22722)

68 Barnes MS, Bonham MP, Robson PJ, Strain JJ, Lowe-Strong AS, Eaton-Evans J, Ginty F & Wallace JM. Assessment of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D3 concentrations in male and female multiple sclerosis patients and control volunteers. *Multiple Sclerosis* 2007 **13** 670–672. (https://doi.org/10.1177/1352458506072666)

69 Smolders J, Menheere P, Kessels A, Damoiseaux J & Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. *Multiple Sclerosis* 2008 **14** 1220–1224. (https://doi.org/10.1177/1352458508094399)

70 Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, Calvo MS, Cashman KD, Combs G, De-Regil LM, *et al.* Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Annals of the New York Academy of Sciences* 2018 **1430** 44–79. (https://doi.org/10.1111/nyas.13968)

71 Cashman KD, Dowling KG, Skrabakova Z, Gonzalez-Gross M, Valtuena J, De Henauw S, Moreno L, Damsgaard CT, Michaelsen KF, Molgaard C, *et al.* Vitamin D deficiency in Europe: pandemic? *American Journal of Clinical Nutrition* 2016 **103** 1033–1044. (https://doi.org/10.3945/ajcn.115.120873)

72 Holick MF. Vitamin D deficiency. *New England Journal of Medicine* 2007 **357** 266–281. (https://doi.org/10.1056/NEJMra070553)

73 Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, Tulchinsky T, Thacher TD, Marton T & Hogler W. Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. *BMC Pediatrics* 2018 **18** 183. (https://doi.org/10.1186/s12887-018-1159-y)

74 Hassan-Smith ZK, Hewison M & Gittoes NJ. Effect of vitamin D deficiency in developed countries. *British Medical Bulletin* 2017 **122** 79–89. (https://doi.org/10.1093/bmb/ldx005)

75 Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, *et al.* Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet* 2010 **376** 180–188. (https://doi.org/10.1016/S0140-6736(10)60588-0)

76 Jiang X, Kiel DP & Kraft P. The genetics of vitamin D. *Bone* 2019 **126** 59–77. (https://doi.org/10.1016/j.bone.2018.10.006)

77 Jiang X, O'Reilly PF, Aschard H, Hsu YH, Richards JB, Dupuis J, Ingelsson E, Karasik D, Pilz S, Berry D, *et al.* Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. *Nature Communications* 2018 **9** 260. (https://doi.org/10.1038/s41467-017-02662-2)

78 Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, Goltzman D, Leong A, Greenwood CM, Thanassoulis G & Richards JB. Vitamin D and risk of multiple sclerosis: a Mendelian randomization study. *PLoS Medicine* 2015 **12** e1001866. (https://doi.org/10.1371/journal.pmed.1001866)

79 Rhead B, Baarnhielm M, Gianfrancesco M, Mok A, Shao X, Quach H, Shen L, Schaefer C, Link J, Gyllenberg A, *et al.* Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk. *Neurology: Genetics* 2016 **2** e97. (https://doi.org/10.1212/NXG.0000000000000097)

80 Hahn J, Cook NR, Alexander EK, Friedman S, Walter J, Bubes V, Kotler G, Lee IM, Manson JE & Costenbader KH. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* 2022 **376** e066452. (https://doi.org/10.1136/bmj-2021-066452)

81 Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, *et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 53–58. (https://doi.org/10.1210/jc.2010-2704)

82 Postlethwaite AE, Tuckey RC, Kim TK, Li W, Bhattacharya SK, Myers LK, Brand DD & Slominski AT. 20S-Hydroxyvitamin D3, a secosteroid produced in humans, is anti-inflammatory and inhibits murine autoimmune arthritis. *Frontiers in Immunology* 2021 **12** 678487. (https://doi.org/10.3389/fimmu.2021.678487)

83 Bae SC & Lee YH. Vitamin D level and risk of systemic lupus erythematosus and rheumatoid arthritis: a Mendelian randomization. *Clinical Rheumatology* 2018 **37** 2415–2421. (https://doi.org/10.1007/s10067-018-4152-9)

84 Viatte S, Yarwood A, McAllister K, Al-Mudhaffer S, Fu B, Flynn E, Symmons DP, Young A & Barton A. The role of genetic polymorphisms regulating vitamin D levels in rheumatoid arthritis outcome: a Mendelian randomisation approach. *Annals of the Rheumatic Diseases* 2014 **73** 1430–1433. (https://doi.org/10.1136/annrheumdis-2013-204972)

85 Bagheri-Hosseinabadi Z, Imani D, Yousefi H & Abbasifard M. Vitamin D receptor (VDR) gene polymorphism and risk of rheumatoid arthritis (RA): systematic review and meta-analysis. *Clinical Rheumatology* 2020 **39** 3555–3569. (https://doi.org/10.1007/s10067-020-05143-y)

86 Yan X, Zhao Y, Pan J, Fang K, Wang Y, Li Z & Chang X. Vitamin D-binding protein (group-specific component) has decreased expression in rheumatoid arthritis. *Clinical and Experimental Rheumatology* 2012 **30** 525–533.

87 Kuo CY, Huang YC, Lin KJ & Tsai TY. Vitamin D deficiency is associated with severity of dry eye symptoms and primary Sjogren's syndrome: a systematic review and meta-analysis. *Journal of Nutritional Science and Vitaminology* 2020 **66** 386–388. (https://doi.org/10.3177/jnsv.66.386)

88 Li L, Chen J & Jiang Y. The association between vitamin D level and Sjogren's syndrome: a meta-analysis. *International Journal of Rheumatic Diseases* 2019 **22** 532–533. (https://doi.org/10.1111/1756-185X.13474)

89 Erten Ş, Sahin A, Altunoglu A, Gemcioglu E & Koca C. Comparison of plasma vitamin D levels in patients with Sjogren's syndrome and healthy subjects. *International Journal of Rheumatic Diseases* 2015 **18** 70–75. (https://doi.org/10.1111/1756-185X.12298)

90 Arshad A, Mahmood SBZ, Ayaz A, Al Karim Manji A & Ahuja AK. Association of vitamin D deficiency and disease activity in systemic

lupus erythematosus patients: two-year follow-up study. *Archives of Rheumatology* 2021 **36** 101–106. (https://doi.org/10.46497/ArchRheumatol.2021.8178)
91 Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW & Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. *Autoimmunity Reviews* 2006 **5** 114–117. (https://doi.org/10.1016/j.autrev.2005.05.009)
92 Dall'Ara F, Cutolo M, Andreoli L, Tincani A & Paolino S. Vitamin D and systemic lupus erythematous: a review of immunological and clinical aspects. *Clinical and Experimental Rheumatology* 2018 **36** 153–162.
93 Chen XE, Chen P, Chen SS, Lu J, Ma T, Shi G, Zhou Y, Li J & Sheng L. A population association study of vitamin D receptor gene polymorphisms and haplotypes with the risk of systemic lupus erythematosus in a Chinese population. *Immunologic Research* 2017 **65** 750–756. (https://doi.org/10.1007/s12026-017-8914-2)
94 Fakhfakh R, Feki S, Elleuch A, Neifar M, Marzouk S, Elloumi N, Hachicha H, Abida O, Bahloul Z, Ayadi F, *et al.* Vitamin D status and CYP27B1-1260 promoter polymorphism in Tunisian patients with systemic lupus erythematosus. *Molecular Genetics and Genomic Medicine* 2021 **9** e1618. (https://doi.org/10.1002/mgg3.1618)
95 Del Pinto R, Pietropaoli D, Chandar AK, Ferri C & Cominelli F. Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. *Inflammatory Bowel Diseases* 2015 **21** 2708–2717. (https://doi.org/10.1097/MIB.0000000000000546)
96 Gubatan J, Chou ND, Nielsen OH & Moss AC. Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2019 **50** 1146–1158. (https://doi.org/10.1111/apt.15506)
97 Lund-Nielsen J, Vedel-Krogh S, Kobylecki CJ, Brynskov J, Afzal S & Nordestgaard BG. Vitamin D and inflammatory bowel disease: Mendelian randomization analyses in the Copenhagen studies and UK Biobank. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 3267–3277. (https://doi.org/10.1210/jc.2018-00250)
98 Gisbert-Ferrandiz L, Salvador P, Ortiz-Masia D, Macias-Ceja DC, Orden S, Esplugues JV, Calatayud S, Hinojosa J, Barrachina MD & Hernandez C. A single nucleotide polymorphism in the vitamin D receptor gene is associated with decreased levels of the protein and a penetrating pattern in Crohn's disease. *Inflammatory Bowel Diseases* 2018 **24** 1462–1470. (https://doi.org/10.1093/ibd/izy094)
99 Eloranta JJ, Wenger C, Mwinyi J, Hiller C, Gubler C, Vavricka SR, Fried M, Kullak-Ublick GA & Swiss IBD Cohort Study Group. Association of a common vitamin D-binding protein polymorphism with inflammatory bowel disease. *Pharmacogenetics and Genomics* 2011 **21** 559–564. (https://doi.org/10.1097/FPC.0b013e328348f70c)
100 Sintzel MB, Rametta M & Reder AT. Vitamin D and multiple sclerosis: a comprehensive review. *Neurology and Therapy* 2018 **7** 59–85. (https://doi.org/10.1007/s40120-017-0086-4)
101 Harroud A & Richards JB. Mendelian randomization in multiple sclerosis: a causal role for vitamin D and obesity? *Multiple Sclerosis* 2018 **24** 80–85. (https://doi.org/10.1177/1352458517737373)
102 Sundqvist E, Baarnhielm M, Alfredsson L, Hillert J, Olsson T & Kockum I. Confirmation of association between multiple sclerosis and CYP27B1. *European Journal of Human Genetics* 2010 **18** 1349–1352. (https://doi.org/10.1038/ejhg.2010.113)
103 Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, Chao MJ, Vieth R, Sadovnick AD & Ebers GC. Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. *American Journal of Clinical Nutrition* 2008 **88** 441–447. (https://doi.org/10.1093/ajcn/88.2.441)
104 Scazzone C, Agnello L, Ragonese P, Lo Sasso B, Bellia C, Bivona G, Schillaci R, Salemi G & Ciaccio M. Association of CYP2R1 rs10766197 with MS risk and disease progression. *Journal of Neuroscience Research* 2018 **96** 297–304. (https://doi.org/10.1002/jnr.24133)
105 Agliardi C, Guerini FR, Zanzottera M, Bolognesi E, Costa AS & Clerici M. Vitamin D-binding protein gene polymorphisms are not associated with MS risk in an Italian cohort. *Journal of Neuroimmunology* 2017 **305** 92–95. (https://doi.org/10.1016/j.jneuroim.2017.02.009)
106 Scazzone C, Agnello L, Bivona G, Lo Sasso B & Ciaccio M. Vitamin D and genetic susceptibility to multiple sclerosis. *Biochemical Genetics* 2021 **59** 1–30. (https://doi.org/10.1007/s10528-020-10010-1)
107 Hou Y, Song A, Jin Y, Xia Q, Song G & Xing X. A dose-response meta-analysis between serum concentration of 25-hydroxy vitamin D and risk of type 1 diabetes mellitus. *European Journal of Clinical Nutrition* 2021 **75** 1010–1023. (https://doi.org/10.1038/s41430-020-00813-1)
108 Feng R, Li Y, Li G, Li Z, Zhang Y, Li Q & Sun C. Lower serum 25 (OH) D concentrations in type 1 diabetes: a meta-analysis. *Diabetes Research and Clinical Practice* 2015 **108** e71–e75. (https://doi.org/10.1016/j.diabres.2014.12.008)
109 Manousaki D, Harroud A, Mitchell RE, Ross S, Forgetta V, Timpson NJ, Smith GD, Polychronakos C & Richards JB. Vitamin D levels and risk of type 1 diabetes: a Mendelian randomization study. *PLoS Medicine* 2021 **18** e1003536. (https://doi.org/10.1371/journal.pmed.1003536)
110 Nejentsev S, Cooper JD, Godfrey L, Howson JM, Rance H, Nutland S, Walker NM, Guja C, Ionescu-Tirgoviste C, Savage DA, *et al.* Analysis of the vitamin D receptor gene sequence variants in type 1 diabetes. *Diabetes* 2004 **53** 2709–2712. (https://doi.org/10.2337/diabetes.53.10.2709)
111 Almeida JT, Rodrigues D, Guimaraes J & Lemos MC. Vitamin D pathway genetic variation and type 1 diabetes: a case-control association study. *Genes* 2020 **11** 897. (https://doi.org/10.3390/genes11080897)
112 Elf K, Askmark H, Nygren I & Punga AR. Vitamin D deficiency in patients with primary immune-mediated peripheral neuropathies. *Journal of the Neurological Sciences* 2014 **345** 184–188. (https://doi.org/10.1016/j.jns.2014.07.040)
113 Fu H, Tang Z, Wang Y, Ding X, Rinaldi G, Rahmani J & Xing F. Relationship between vitamin D level and mortality in adults with psoriasis: a retrospective cohort study of NHANES data. *Clinical Therapeutics* 2021 **43** e33–e38. (https://doi.org/10.1016/j.clinthera.2020.11.016)
114 Pitukweerakul S, Thavaraputta S, Prachuapthunyachart S & Karnchanasorn R. Hypovitaminosis D is associated with psoriasis: a systematic review and meta-analysis. *Kansas Journal of Medicine* 2019 **12** 103–108. (https://doi.org/10.17161/kjm.v12i4.13255)
115 Hambly R & Kirby B. The relevance of serum vitamin D in psoriasis: a review. *Archives of Dermatological Research* 2017 **309** 499–517. (https://doi.org/10.1007/s00403-017-1751-2)
116 Liu J, Wang W, Liu K, Wan D, Wu Z, Cao Z, Luo Y, Xiao C & Yin M. Vitamin D receptor gene polymorphisms are associated with psoriasis susceptibility and the clinical response to calcipotriol in psoriatic patients. *Experimental Dermatology* 2020 **29** 1186–1190. (https://doi.org/10.1111/exd.14202)
117 Ke W, Sun T, Zhang Y, He L, Wu Q, Liu J & Zha B. 25-Hydroxyvitamin D serum level in Hashimoto's thyroiditis, but not Graves' disease is relatively deficient. *Endocrine Journal* 2017 **64** 581–587. (https://doi.org/10.1507/endocrj.EJ16-0547)
118 Xu MY, Cao B, Yin J, Wang DF, Chen KL & Lu QB. Vitamin D and Graves' disease: a meta-analysis update. *Nutrients* 2015 **7** 3813–3827. (https://doi.org/10.3390/nu7053813)
119 Wang J, Lv S, Chen G, Gao C, He J, Zhong H & Xu Y. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* 2015 **7** 2485–2498. (https://doi.org/10.3390/nu7042485)
120 Zhou F, Liang Z, Wang X, Tan G, Wei W, Zheng G, Ma X, Tian D, Li H & Yu H. The VDR gene confers a genetic predisposition to Graves' disease and Graves' ophthalmopathy in the Southwest Chinese Han population. *Gene* 2021 **793** 145750. (https://doi.org/10.1016/j.gene.2021.145750)
121 Meng S, He ST, Jiang WJ, Xiao L, Li DF, Xu J, Shi XH & Zhang JA. Genetic susceptibility to autoimmune thyroid diseases in a Chinese Han population: role of vitamin D receptor gene polymorphisms.

Annales d'Endocrinologie 2015 **76** 684–689. (https://doi.org/10.1016/j.ando.2015.01.003)
122 Jennings CE, Owen CJ, Wilson V & Pearce SH. A haplotype of the CYP27B1 promoter is associated with autoimmune Addison's disease but not with Graves' disease in a UK population. *Journal of Molecular Endocrinology* 2005 **34** 859–863. (https://doi.org/10.1677/jme.1.01760)
123 Justo ME, Aldecoa M, Cela E, Leoni J, Gonzalez Maglio DH, Villa AM, Aguirre F & Paz ML. Low vitamin D serum levels in a cohort of myasthenia gravis patients in Argentina. *Photochemistry and Photobiology* 2021 **97** 1145–1149. (https://doi.org/10.1111/php.13432)
124 Kang SY, Kang JH, Choi JC, Song SK & Oh JH. Low serum vitamin D levels in patients with myasthenia gravis. *Journal of Clinical Neuroscience* 2018 **50** 294–297. (https://doi.org/10.1016/j.jocn.2018.01.047)
125 Askmark H, Haggard L, Nygren I & Punga AR. Vitamin D deficiency in patients with myasthenia gravis and improvement of fatigue after supplementation of vitamin D3: a pilot study. *European Journal of Neurology* 2012 **19** 1554–1560. (https://doi.org/10.1111/j.1468-1331.2012.03773.x)
126 Han JL, Yue YX, Gao X, Xie YC, Hao HJ, Li HY, Yu XL, Li J, Duan RS & Li HF. Vitamin D receptor polymorphism and myasthenia gravis in Chinese Han population. *Frontiers in Neurology* 2021 **12** 604052. (https://doi.org/10.3389/fneur.2021.604052)
127 Korkmaz FN, Ozen G, Unal AU, Odabasi A, Can M, Asicioglu E, Tuglular S & Direskeneli H. Vitamin D levels in patients with small and medium vessel vasculitis. *Reumatologia Clinica* 2021 **18** 141–146. (https://doi.org/10.1016/j.reuma.2020.11.004)
128 Yoon T, Ahn SS, Pyo JY, Song JJ, Park YB & Lee SW. Serum vitamin D level correlates with disease activity and health-related quality of life in antineutrophil cytoplasmic antibody-associated vasculitis. *Zeitschrift für Rheumatologie* 2022 **81** 77–84. (https://doi.org/10.1007/s00393-020-00949-2)
129 Khabbazi A, Ghojazadeh M, Hajebrahimi S & Nikniaz Z. Relationship between vitamin D level and Bechcet's disease activity: a systematic review and meta-analysis. *International Journal for Vitamin and Nutrition Research* 2020 **90** 527–534. (https://doi.org/10.1024/0300-9831/a000542)
130 Zhong Z, Su G, Du L, Zhou Q, Li F, Chi W, Liu S, Zhang M, Zuo X & Yang P. Higher 25-hydroxyvitamin D level is associated with increased risk for Behcet's disease. *Clinical Nutrition* 2021 **40** 518–524. (https://doi.org/10.1016/j.clnu.2020.05.049)
131 Cantorna MT, Hayes CE & DeLuca HF. 1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. *Journal of Nutrition* 1998 **128** 68–72. (https://doi.org/10.1093/jn/128.1.68)
132 Zhou L, Wang J, Li J, Li T, Chen Y, June RR & Zheng SG. 1,25-Dihydroxyvitamin D3 ameliorates collagen-induced arthritis via suppression of Th17 cells through miR-124 mediated inhibition of IL-6 signaling. *Frontiers in Immunology* 2019 **10** 178. (https://doi.org/10.3389/fimmu.2019.00178)
133 Galea R, Nel HJ, Talekar M, Liu X, Ooi JD, Huynh M, Hadjigol S, Robson KJ, Ting YT, Cole S, *et al.* PD-L1- and calcitriol-dependent liposomal antigen-specific regulation of systemic inflammatory autoimmune disease. *JCI Insight* 2019 **4** e126025. (https://doi.org/10.1172/jci.insight.126025)
134 Zwerina K, Baum W, Axmann R, Heiland GR, Distler JH, Smolen J, Hayer S, Zwerina J & Schett G. Vitamin D receptor regulates TNF-mediated arthritis. *Annals of the Rheumatic Diseases* 2011 **70** 1122–1129. (https://doi.org/10.1136/ard.2010.142331)
135 Gu X, Gu B, Lv X, Yu Z, Wang R, Zhou X, Qiao W, Mao Z, Zuo G, Li Q, *et al.* 1,25-Dihydroxy-vitamin D3 with tumor necrosis factor-alpha protects against rheumatoid arthritis by promoting p53 acetylation-mediated apoptosis via Sirt1 in synoviocytes. *Cell Death and Disease* 2016 **7** e2423. (https://doi.org/10.1038/cddis.2016.300)
136 Reynolds JA, Rosenberg AZ, Smith CK, Sergeant JC, Rice GI, Briggs TA, Bruce IN & Kaplan MJ. Brief Report: Vitamin D deficiency is associated with endothelial dysfunction and increases type I interferon gene expression in a murine model of systemic lupus erythematosus. *Arthritis and Rheumatology* 2016 **68** 2929–2935. (https://doi.org/10.1002/art.39803)
137 Yamamoto EA, Nguyen JK, Liu J, Keller E, Campbell N, Zhang CJ, Smith HR, Li X & Jorgensen TN. Low levels of vitamin D promote memory B cells in lupus. *Nutrients* 2020 **12** 291. (https://doi.org/10.3390/nu12020291)
138 Correa Freitas E, Evelyn Karnopp T, de Souza Silva JM, Cavalheiro do Espirito R, da Rosa TH, de Oliveira MS, da Costa Goncalves F, de Oliveira FH, Guilherme Schaefer P & Andre Monticielo O. Vitamin D supplementation ameliorates arthritis but does not alleviates renal injury in pristane-induced lupus model. *Autoimmunity* 2019 **52** 69–77. (https://doi.org/10.1080/08916934.2019.1613383)
139 Lagishetty V, Misharin AV, Liu NQ, Lisse TS, Chun RF, Ouyang Y, McLachlan SM, Adams JS & Hewison M. Vitamin D deficiency in mice impairs colonic antibacterial activity and predisposes to colitis. *Endocrinology* 2010 **151** 2423–2432. (https://doi.org/10.1210/en.2010-0089)
140 Assa A, Vong L, Pinnell LJ, Avitzur N, Johnson-Henry KC & Sherman PM. Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. *Journal of Infectious Diseases* 2014 **210** 1296–1305. (https://doi.org/10.1093/infdis/jiu235)
141 Ryz NR, Lochner A, Bhullar K, Ma C, Huang T, Bhinder G, Bosman E, Wu X, Innis SM, Jacobson K, *et al.* Dietary vitamin D3 deficiency alters intestinal mucosal defense and increases susceptibility to Citrobacter rodentium-induced colitis. *American Journal of Physiology: Gastrointestinal and Liver Physiology* 2015 **309** G730–G742. (https://doi.org/10.1152/ajpgi.00006.2015)
142 Wei X, Li X, Du J, Ge X, Sun Y, Li X, Xun Z, Liu W, Wang ZY & Li YC. Vitamin D deficiency exacerbates colonic inflammation due to activation of the local renin-angiotensin system in the colon. *Digestive Diseases and Sciences* 2021 **66** 3813–3821. (https://doi.org/10.1007/s10620-020-06713-5)
143 Laverny G, Penna G, Vetrano S, Correale C, Nebuloni M, Danese S & Adorini L. Efficacy of a potent and safe vitamin D receptor agonist for the treatment of inflammatory bowel disease. *Immunology Letters* 2010 **131** 49–58. (https://doi.org/10.1016/j.imlet.2010.03.006)
144 Ooi JH, Li Y, Rogers CJ & Cantorna MT. Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. *Journal of Nutrition* 2013 **143** 1679–1686. (https://doi.org/10.3945/jn.113.180794)
145 Yoo JS, Park CY, Seo YK, Woo SH, Kim DY & Han SN. Vitamin D supplementation partially affects colonic changes in dextran sulfate sodium-induced colitis obese mice but not lean mice. *Nutrition Research* 2019 **67** 90–99. (https://doi.org/10.1016/j.nutres.2019.03.009)
146 Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE & Cantorna MT. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. *Molecular Endocrinology* 2003 **17** 2386–2392. (https://doi.org/10.1210/me.2003-0281)
147 Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M & Li YC. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *American Journal of Physiology: Gastrointestinal and Liver Physiology* 2008 **294** G208–G216. (https://doi.org/10.1152/ajpgi.00398.2007)
148 Liu N, Nguyen L, Chun RF, Lagishetty V, Ren S, Wu S, Hollis B, Deluca HF, Adams JS & Hewison M. Altered endocrine and autocrine metabolism of vitamin D in a mouse model of gastrointestinal inflammation. *Endocrinology* 2008 **149** 4799–4808. (https://doi.org/10.1210/en.2008-0060)
149 Kim JH, Yamaori S, Tanabe T, Johnson CH, Krausz KW, Kato S & Gonzalez FJ. Implication of intestinal VDR deficiency in inflammatory bowel disease. *Biochimica et Biophysica Acta* 2013 **1830** 2118–2128. (https://doi.org/10.1016/j.bbagen.2012.09.020)
150 Lu R, Zhang YG, Xia Y, Zhang J, Kaser A, Blumberg R & Sun J. Paneth cell alertness to pathogens maintained by vitamin D receptors.

Gastroenterology 2021 **160** 1269–1283. (https://doi.org/10.1053/j.gastro.2020.11.015)
151 DeLuca HF & Plum LA. Vitamin D deficiency diminishes the severity and delays onset of experimental autoimmune encephalomyelitis. *Archives of Biochemistry and Biophysics* 2011 **513** 140–143. (https://doi.org/10.1016/j.abb.2011.07.005)
152 Wang Y, Marling SJ, Zhu JG, Severson KS & DeLuca HF. Development of experimental autoimmune encephalomyelitis (EAE) in mice requires vitamin D and the vitamin D receptor. *PNAS* 2012 **109** 8501–8504. (https://doi.org/10.1073/pnas.1206054109)
153 Fernandes de Abreu DA, Landel V, Barnett AG, McGrath J, Eyles D & Feron F. Prenatal vitamin D deficiency induces an early and more severe experimental autoimmune encephalomyelitis in the second generation. *International Journal of Molecular Sciences* 2012 **13** 10911–10919. (https://doi.org/10.3390/ijms130910911)
154 Cantorna MT, Hayes CE & DeLuca HF. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *PNAS* 1996 **93** 7861–7864. (https://doi.org/10.1073/pnas.93.15.7861)
155 Spach KM, Pedersen LB, Nashold FE, Kayo T, Yandell BS, Prolla TA & Hayes CE. Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis. *Physiological Genomics* 2004 **18** 141–151. (https://doi.org/10.1152/physiolgenomics.00003.2004)
156 Spach KM, Nashold FE, Dittel BN & Hayes CE. IL-10 signaling is essential for 1,25-dihydroxyvitamin D3-mediated inhibition of experimental autoimmune encephalomyelitis. *Journal of Immunology* 2006 **177** 6030–6037. (https://doi.org/10.4049/jimmunol.177.9.6030)
157 Mayne CG, Spanier JA, Relland LM, Williams CB & Hayes CE. 1,25-Dihydroxyvitamin D3 acts directly on the T lymphocyte vitamin D receptor to inhibit experimental autoimmune encephalomyelitis. *European Journal of Immunology* 2011 **41** 822–832. (https://doi.org/10.1002/eji.201040632)
158 Wang Y, Marling SJ, Martino VM, Prahl JM & Deluca HF. The absence of 25-hydroxyvitamin D3-1alpha-hydroxylase potentiates the suppression of EAE in mice by ultraviolet light. *Journal of Steroid Biochemistry and Molecular Biology* 2016 **163** 98–102. (https://doi.org/10.1016/j.jsbmb.2016.04.010)
159 Giulietti A, Gysemans C, Stoffels K, van Etten E, Decallonne B, Overbergh L, Bouillon R & Mathieu C. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice. *Diabetologia* 2004 **47** 451–462. (https://doi.org/10.1007/s00125-004-1329-3)
160 Mathieu C, van Etten E, Decallonne B, Guilietti A, Gysemans C, Bouillon R & Overbergh L. Vitamin D and 1,25-dihydroxyvitamin D3 as modulators in the immune system. *Journal of Steroid Biochemistry and Molecular Biology* 2004 **89–90** 449–452 449–452. (https://doi.org/10.1016/j.jsbmb.2004.03.014)
161 Zella JB, McCary LC & DeLuca HF. Oral administration of 1,25-dihydroxyvitamin D3 completely protects NOD mice from insulin-dependent diabetes mellitus. *Archives of Biochemistry and Biophysics* 2003 **417** 77–80. (https://doi.org/10.1016/s0003-9861(03)00338-2)
162 Mathieu C, Van Etten E, Gysemans C, Decallonne B, Kato S, Laureys J, Depovere J, Valckx D, Verstuyf A & Bouillon R. In vitro and in vivo analysis of the immune system of vitamin D receptor knockout mice. *Journal of Bone and Mineral Research* 2001 **16** 2057–2065. (https://doi.org/10.1359/jbmr.2001.16.11.2057)
163 Gysemans C, van Etten E, Overbergh L, Giulietti A, Eelen G, Waer M, Verstuyf A, Bouillon R & Mathieu C. Unaltered diabetes presentation in NOD mice lacking the vitamin D receptor. *Diabetes* 2008 **57** 269–275. (https://doi.org/10.2337/db07-1095)
164 Morro M, Vila L, Franckhauser S, Mallol C, Elias G, Ferre T, Molas M, Casana E, Rodo J, Pujol A, *et al.* Vitamin D receptor overexpression in beta-cells ameliorates diabetes in mice. *Diabetes* 2020 **69** 927–939. (https://doi.org/10.2337/db19-0757)
165 Viloria K, Nasteska D, Briant LJB, Heising S, Larner DP, Fine NHF, Ashford FB, da Silva Xavier G, Ramos MJ, Hasib A, *et al.* Vitamin-D-binding protein contributes to the maintenance of alpha cell function and glucagon secretion. *Cell Reports* 2020 **31** 107761. (https://doi.org/10.1016/j.celrep.2020.107761) 107761.
166 Kong J, Grando SA & Li YC. Regulation of IL-1 family cytokines IL-1alpha, IL-1 receptor antagonist, and IL-18 by 1,25-dihydroxyvitamin D3 in primary keratinocytes. *Journal of Immunology* 2006 **176** 3780–3787. (https://doi.org/10.4049/jimmunol.176.6.3780)
167 Misharin A, Hewison M, Chen CR, Lagishetty V, Aliesky HA, Mizutori Y, Rapoport B & McLachlan SM. Vitamin D deficiency modulates Graves' hyperthyroidism induced in BALB/c mice by thyrotropin receptor immunization. *Endocrinology* 2009 **150** 1051–1060. (https://doi.org/10.1210/en.2008-1191)
168 Choi B, Lee ES & Sohn S. Vitamin D3 ameliorates herpes simplex virus-induced Behcet's disease-like inflammation in a mouse model through down-regulation of toll-like receptors. *Clinical and Experimental Rheumatology* 2011 **29** (Supplement 67) S13–S19.

Received in final form 3 February 2022
Accepted 23 February 2022
Accepted Manuscript published online 23 February 2022