# Vitamin D, infections and immunity

## *Witamina D, zakażenia i odporność*

*Waldemar Misiorowski*

*Department of Endocrinology, Center of Postgraduate Medical Education, Bielański Hospital, Warsaw, Poland*

KEYWORDS:

- vitamin D
- immune system
- infections
- autoagression

ABSTRACT

Vitamin D (VD) is a steroid prohormone that regulates the body's calcium and phosphate levels in bone mineralization. It is also well described as a fat-soluble vitamin playing an important role in immunomodulation, regulation of cytokines, and cell proliferation. Thus, VD is a powerful hormone with pleiotropic effects, which acts to maintain optimal health. Recent studies demonstrate that VD deficiency is associated with the development of autoimmune disorders. Vitamin D generates many extraskeletal effects due to the vitamin D receptor (VDR) which is present in most tissues throughout the body. This paper reviews the recent data on the role of vitamin D in the genesis of various immunological disorders. The possible role of vitamin D in infections is implied from its impact on the innate and adaptive immune responses. A significant effect is the suppression of inflammatory processes. It inhibits immune reactions in general, but it enhances the transcription of "endogenous antibiotics" such as cathelicidin and defensins. VD inhibits the genesis of both Th1 – and Th2-cell mediated diseases. Th1 – dependent autoimmune diseases (e.g., multiple sclerosis, Type 1 diabetes, Crohn's disease, rheumatoid arthritis and so on) are also inhibited by VD due to inhibition of antigen presentation, reduced polarization of Th0 cells to Th1 cells and reduced production of cytokines from the latter cells. VD seems to also be a useful adjunct in the prevention of allograft rejection. Cardiac and coagulopathic features of COVID-19 disease deserve attention as they may be related to vitamin D. There are also intriguing potential links to vitamin D as a factor in the cytokine storm that consist some of the most serious consequences of SARS-CoV-2 infection, such as the acute respiratory distress syndrome. Finally, the current clinical data strongly associate vitamin D with SARS-CoV-2 infection, however a putative clinical link that at this time must still be considered hypothetical.

SŁOWA KLUCZOWE:

- witamina D
- układ immunologiczny
- zakażenia
- autoagresja

STRESZCZENIE

Witamina D (VD) to steroidowy prohormon, uczestniczący w regulacji homeostazy wapniowo-fosforanowej, kluczowy dla mineralizacji kości. W ostatnich latach wykazano także szereg pozakostnych działań witaminy D, m.in. ważną rolę w immunomodulacji, regulacji produkcji cytokin i proliferacji i różnicowaniu się komórek układu odpornościowego. Niedobór VD jest związany z podatnością na zakażenia wirusowe i bakteryjne a także zwiększonym ryzykiem rozwoju chorób autoimmunologicznych. W niniejszej pracy dokonano przeglądu danych na temat roli witaminy D w genezie różnych zaburzeń immunologicznych. Możliwa rola witaminy D w zwalczaniu zakażeń wynika z jej modyfikującego wpływu na bierną i czynną odpowiedzi immunologiczne. Istotnym działaniem witaminy D jest hamowanie procesów zapalnych, ale jednocześnie zwiększa transkrypcję "endogennych antybiotyków", takich jak katelicydyna i defensyny. VD zmniejsza prezentację antygenów przez komórki dendrytyczne, hamuje polaryzację komórek Th0 do komórek Th1 lub -2 i ogranicza produkcję cytokin prozapalnych, zwłaszcza INFγ, a jednocześnie ułatwia tworzenie się Treg, co w efekcie ogranicza i umożliwia wygaśnięcie reakcji immunologicznej. Istnieją dane wskazujące że VD może łagodzić objawy chorób autoimmunologicznych zależnych od Th1 (np. stwardnienie rozsiane, cukrzyca typu 1, choroba Leśniowskiego-Crohna, reumatoidalne zapalenie stawów itp.) w modelach zwierzęcych i u ludzi. VD wydaje się być również użytecznym uzupełnieniem w zapobieganiu odrzuceniu przeszczepu. Na uwagę zasługują sercowo-naczyniowe i zakrzepowe elementy choroby SARS-CoV-2, które mogą być łączone z gorszym zaopatrzeniem w witaminę D. Istnieją również dane wskazujące na rolę niedoboru witaminy D w patogenezie "burzy cytokinowej", jedną z najpoważniejszych konsekwencji zakażenia COVID-19. Należy jednak podkreślić, że pomimo coraz liczniejszych danych klinicznych silnie łączących witaminę D z ryzykiem i przebiegiem infekcji SARS-CoV-2, to muszą one być traktowane z ostrożnością, a domniemany związek powinien być nadal uważany za hipotetyczny.

*Address for correspondence: * Waldemar Misiorowski, Department of Endocrinology, Center of Postgraduate Medical Education, Bielański Hospital, Cegłowska 80 Street, 01-809 Warsaw, Poland, e-mail: wmisiorowski@cmkp.edu.pl*

*ISSN 2657-9669/* 

*Published and financed by Centre of Postgraduate Medical Education; https://doi.org/10.36553/wm.55*

## Introduction

A significant segment of the population has vitamin D (VD) hypovitaminosis, which frequently does not induce visible clinical manifestations. VD hypovitaminosis may be the consequence of lack of sunshine, inadequate diet, low levels of high-density cholesterol, as well as obesity. However, many people have a genetic disposition to VD hypovitaminosis, which may be a more important factor than exposure to sunshine and/or dietary intake of vitamin $D_3$ (1-4). In the multicenter study by Wang et al. (including ~30,000 subjects), single nucleotide polymorphisms in four genes has been found to be associated with relative VD hypovitaminosis (1). Similar data have been obtained by other groups examining other different ethnic populations (2-4).

Over the last few decades, it came to light that vitamin D (VD), besides its well-known functions in bone homeostasis, plays a basic role in the regulation of immune functions (5, 6). It inhibits carcinogenesis and enhances production of endogenous antimicrobial "antibiotics" (7). This review deals only with a narrow segment of extra-bone effects of VD, notably with its physiological role in regulation of immune functions.

## Modulation of Immune Functions in General

The immune effects of VD (calcitriol and vitamin D receptor VDR) in the healthy organism are highly complex. 1α-hydroxylase can be found not only in the kidney but also in the immune system, primarily in the lymphocytes, monocytes, dendritic cells (DCs) and elsewhere, even in the bronchial wall (8). Moreover, the VDR, which has also been detected in immunological cells, suggests that vitamin D can directly regulate some processes related to immunity.

Activated human T and B cells and also the endothelial cells lining the upper and lower respiratory tract also express CYP27B1 and can transform inactive metabolite 25(OH)D into active $1,25(OH)_2D$ (calcitriol). In general, the epithelia are the first responders to invading pathogens sounding the alarm, via their own innate immune system, to activate dendritic cells and macrophages and to recruit neutrophils and T cells to the site of infection. In the setting of vitamin D deficiency, immune responses would be impaired because less 25-OH D would be available for synthesis of $1,25(OH)_2D$, leading to impairment of innate immune function (9). This localized, intracrine, mechanism is now considered a cornerstone of the interaction between vitamin D and the immune system. It is quite distinct from the endocrine actions of vitamin D concerned with regulating mineral homeostasis. While parathormone enhances the expression of 1α-hydroxylase in the kidney, the activity 1α-hydroxylase of in the immune system is mostly regulated by certain immune inputs including IFN-γ and Toll-like receptors, which recognize molecular patterns on the surface of certain microbes, primarily lipopolysaccharides, lipoproteins and other components of mostly Gram-negative bacteria (10-13). In monocytes, the expression of 1α-hydroxylase requires the simultaneous activation of JAK-STAT, NF-κB and p38-MAPK pathways. For activation of 1α-hydroxylase, generally at least two stimuli are needed; most commonly IFN-γ + lipopolysaccharides or Janus kinase-signal transducer-activator or MAPK or NF-κB or something else. In fact, induction of 1α-hydroxylase is preceded by enhanced liberation of IL-1 and TNF-α, that is, cytokines responsible for the early phase of inflammation. Therefore, enhanced production of calcitriol may be considered a late event in inflammation, a kind of negative feedback loop, which helps to terminate the inflammatory cascade (11).

## Vitamin D and infections

The possible role of vitamin D in infectious diseases is implied by its impact on the innate and adaptive immune responses. The innate immune response can be defined, generally, as nonspecific, although it proves to be the first line of defense against infective agents and initiates antigen presentation (14, 15). The crucial points for the innate immune response are the Toll-like receptors (TLRs), being a subgroup of various intracellular innate Pathogen Recognition Receptors (PRRs), which is present in macrophages, polymorphonuclear cells, monocytes, and epithelial cells. TLRs recognize molecules related to the pathogen: the lipopolysaccharides of bacteria or viral proteins and nucleic acids. Such activated TLRs release cytokines which induce reactive oxygen species and antimicrobial peptides (AMPs), cathelicidins, and defensins (16-20). VDR suppresses the expression of Toll-like receptor proteins 2 and 4, and downregulates the Toll-like receptors in the monocytes (21). One of the features of the antibacterial innate response is the destruction of the pathogens by autophagy (22). This process is especially important for the antibacterial response induced by vitamin D against Mycobacterium tuberculosis infection. VD enhances the transcription of certain "endogenous antibiotics" (7). More precisely, VDR directly facilitates the expression of the camp and defB2 genes hence the transcription of antimicrobial peptides cathelicidin and various β-defensins (23-33). Both have antimicrobial effects against various Gram-positive and -negative bacteria, as well as against fungi and certain viruses. Cathelicidin is effective even against antibiotic resistant Pseudomonas aeruginosa (7) and Mycobacterium tuberculosis (32, 33). The ability of macrophages to produce cathelicidin correlated well with the serum 25-OH D concentration (34, 35). Although the antimicrobial function of cathelicidin is crucial, this protein has a number of other functions including the induction of a variety of proinflammatory cytokines, stimulation of the chemotaxis of neutrophils, monocytes, macrophages, and T cells into the site of infection, and promotion of the clearance of respiratory pathogens by inducing apoptosis and autophagy of infected epithelial cells (18, 36). The induction of cathelicidin by $1,25(OH)_2D$ is observed only in higher primates, and it appears, that the ability of vitamin D to promote cathelicidin synthesis is a recent evolutionary development (37). β-defensin 2, such as cathelicidin, contributes to host defense by stimulating the expression of antiviral cytokines and chemokines involved in the recruitment of monocytes/macrophages, natural killer cells, neutrophils, T cells (38). In turn, α-defensins present in vitro efficacy against HIV-1 viruses (27). There are no data indicating that these "endogenous antibiotics" get into the systemic circulation. Therefore, cathelicidin and the various defensins are considered locally acting "natural antibiotics", which protect the mucosal surface of the respiratory and gastrointestinal tracts and the skin (25).

Importantly, vitamin D may have broader antimicrobial actions, including the generation of nitric oxide and superoxide (39, 40). In addition to enhancing monocyte/macrophage antimicrobial functions, vitamin D promotes the killing of pneumococcus by stimulating neutrophils via a range of mechanisms that included upregulation of Toll-like

receptor 2, NOD2, and cathelicidin together with enhanced antimicrobial human neutrophil peptide (HNP1-3) production (41). Even beyond monocytes, macrophages, and neutrophils, which collectively illustrate the importance of vitamin D in supporting a range of innate antibacterial responses, vitamin D can promote antimicrobial function outside the immune system. For example, within the gastrointestinal tract, vitamin D promotes the expression of gap junction proteins that maintain barrier integrity thereby preventing tissue ingress by bacteria from the gut microbiome (42). Similar barrier integrity effects of vitamin D have also been observed for the epithelial cells of the lung (43), along with stimulation of antimicrobial proteins by lung epithelial cells (44, 45).

Upon viral infection, pathogen-associated molecular patterns (PAMPs) can also be recognized by other (PRRs), such as retinoic-acid-inducible gene-I (RIG-I)-like receptors and nucleotide binding-oligomerisation domain (NOD)-like receptors (NLRs). In myeloid and epithelial cells, the intracellular receptor NOD2 is induced by $1,25(OH)_2D$ via two VDREs in the NOD2 gene. The addition of lysosomal breakdown products of bacterial peptidoglycan to calcitriol-induced NOD2 enhanced NF-κB signalling and AMP such as beta defensin 2 expression (46, 47).

VDR inhibits antigen presentation by dendritic cells (DCs). DCs are derived mostly from hemopoietic bone marrow progenitor cells (48). These progenitor cells initially transform into immature DCs. Immature DC cells mature upon phagocytosing, ingesting pathogenic microbes (primarily by oxidative burst) then transforming them into "presentable" MHC class II antigens, they express costimulatory factors such as CD40, CD80 and CD86 and they are already able to migrate into the lymph nodes where they "hand over" the MHC-II complex to T cells. The expression of these cell surface costimulatory factors are inhibited by VD (48). Other DC cells, however, become "tolerogenic", which means losing their ability to phagocytose microbes and to present the MHC-II antigens to Th1 or Th2 cells. VD facilitates formation of tolerogenic DC cells most probably by inhibition of transcription of proteins needed for their phagocytotic and antigen-presenting activities (21, 48-56). In addition to the inhibition of dendritic cell differentiation, that is, reduced expression of MHC complex and costimulatory molecules (48, 57), VD also reduces the total number of DCs most probably by facilitating their spontaneous apoptosis (58).

**Vitamin D, immune system and autoimmunity**

VD inhibits the polarization of naive T0 cells to T1 and to a lesser extent T2 cells, it shifts the balance of Th1/Th2 T cells toward the latter ones, and upregulates Treg cells, the T cells population known to inhibit both Th1 and Th2 cells . Th0 cells primed by DCs may differentiate into one of the three mutually exclusive directions. They will mature into either (1) IFN-γ, TNF-α, IL-1α, IL-1α, IL-2, IL-12 or IL-15-producing cytotoxic Th1 cells responsible not only for the killing of foreign microbes but in many cases also for autoimmune diseases (59, 60), or (2) IL-4, IL-5, IL-6, IL-13-producing Th2 cells, which enhance antibody production in B cells and induce immunoglobulin class switching in B-lymphocytes but also mediate atopic diseases under clinical conditions (59-61), or (3) into mainly IL-10 and TGF-β secreting "central" Treg cells ($CD4^+$ $CD25^+$ Tregs eventually also expressing Foxp3) (62, 63). They are also called "tolerogenic" since they suppress the immune functions in general, including the proliferation of the other two subclasses of Th cells (Th1 and -2) in G1 phase, inhibit IL-2 production, lymphocyte proliferation in general and the delivery of costimulatory signals (48, 49, 53, 64, 65). They are also dubbed "professional" suppressor cells (66). Treg cells constitutively express CTLA-4, which is indispensable for their functional integrity (21, 62, 63). Treg cells have different subtypes and of them the Treg1 cells have really strong immunosuppressant action, that is, they prevent autoimmune diseases and graft rejection (53). Th1 and -2 cells mutually antagonize each other's function and clonal expansion, whereas Treg cells inhibit both of the other subgroups (59-61, 66). **VD inhibits the polarization of Th0 cells to Th1 or -2 cells but facilitates the formation of Tregs** (64, 66). Thus, VD leads the reduced production of of inflammatory cytokines as IFN-γ, IL-17 and IL-21 (61, 67-69). In addition, VD enhances the development of Th2 cells and the production of their characteristic cytokines as IL-4, IL-5 and IL-10, which partly suppresses Th1 function and production of the most important Th1 cytokine IFN-γ (69). The Treg cells, being the "professional" immunosuppressor cells of the body, maintain the self-tolerance (also called peripheral self-tolerance), that is, they protect the organism from autoimmune reactions, among others by inhibiting IL-2 production (50), which is the first step leading to the differentiation of T cells (70).

Evidently, the ratio of differentiation of naive T0 cells to Th1 or Treg cells has tremendous clinical significance (71-75) since, the Th1 induce autoimmune disease, while the Treg cells exert their tolerogenic action by reducing the production of IL-2. As for the regulatory, it is important that the "immunomodulant" (76) VDR favors the differentiation to "tolerogenic" Tregs, more precisely to $CD4^+$ $CD25^+$ $Fox3^+$ cells producing mainly IL-10, TGF-β but less NF-κB and AP-1 than other T cells (66, 77).

A further important effect of VD is the inhibiton of transcription of IL-2 and -12 (78, 79). Reduced transcription of IL-2 (78, 80) seems to be one of the main mechanisms of VD-elicited immunosuppression since transformation of naive $CD4^+$ cells to Th0 cells is the first step of proliferation of lymphocytes. However, probably the most important effect of VD is the inhibition of IFN-γ.

Natural killer T (NKT) cells represent another crucial mechanism of innate immunity and they are important suppressors of autoimmune diseases. VDR is needed for development or maturation of NKTs, which protect the organism from autoimmune diseases (81, 82).

VD ameliorates the disease symptoms of autoimmunity in animal models and in human patients. The importance of VD in physiological protection against autoimmune disorders is proven among others by the finding of Bouillon et al. that VDR-null mice show increased sensitivity to experimental interventions inducing autoimmune diseases (83). In animal experiments, VD showed preventative or therapeutic action, in experimental models of autoimmune diseases such as Type 1 (insulin-responsive) diabetes mellitus (55, 83), multiple sclerosis (84-88), inflammatory bowel disease (89, 90), in experimental models of contact and atopic dermatitis (91). In rheumatoid arthritis, enhanced expression of IL-17 and -22 was observed in human patients (92). Finally, VD induced Treg cells have also been found to inhibit the allograft rejection. The protective action of VD (or its analogs) was due to arrest of Th1 cell infiltration, induction of tolerogenic DCs with simultaneous multiplication of Treg cells, enhanced transcription of TGF-β even that of IL-4, and diminution of the pathologically increased ratio of Th1/2 cells (93-99).

**Vitamin D and COVID-19**

SARS-CoV-2, the virus causing the COVID-19 pandemic had already infected over 15 million people and had caused over 400 000 deaths worldwide (100) and probably, these numbers will grow greatly in the months to come. The search for risk factors predisposing to adverse outcomes of this disease has focused upon age, obesity, diabetes, hypertension, ethnicity, and other factors (101-106). Recently, vitamin D inadequacy has emerged as another potential risk factor (107-109). Although studies of vitamin D and innate immune activity have focused primarily on antibacterial mechanisms, vitamin D can also promote antiviral immunity, which is of great importance in any discussion for its role in COVID-19 infection. This involves a number of mechanisms that overlap with antibacterial responses, such as the induction of cathelicidin and defensins, which can block viral entry into cells as well as suppress viral replication (110, 111). Another property of vitamin D relevant both to antibacterial and antiviral mechanisms are promoting autophagy (112, 113). Autophagy is an essential mechanism by which cells deal with viruses. Autophagic encapsulation of viral particles packages them for lysosomal degradation and subsequent antigen-presentation and adaptive antiviral immune responses (114). Induction of autophagy is a key cellular response to vitamin D, with both 25-OH D and 1,25$(OH)_2$D enhancing expression of the autophagy marker LC3 (36, 41). Thus, autophagy may be sensitive to changes in serum 25-OH D levels. The specific mechanisms by which vitamin D promotes autophagy involves downregulating the mTOR pathway, which inhibits autophagy (116), and by promoting Beclin 1 and PI3KC3, key enzyme drivers of autophagy (117). Upregulation of intracellular Ca and NO by vitamin D also stimulates PI3KC3 activity to promote autophagy (118). Vitamin D-induced autophagy decreases HIV-1 infection (119, 120), influenza A (121), rotavirus (122), and hepatitisC (123). In considering the effects of vitamin D on autophagy, it i s important to recognize that these actions are closely linked to apoptosis, which may aid viral replication. Therefore vitamin D may play a crucial role in maintaining appropriate balance between autophagy and apoptosis to maximize antiviral responses to infection (124).

One of the devastating pathophysiological aspects of SARS-CoV-2 infection is the so-called pulmonary cytokine storm, a major cause of morbidity and mortality. The cytokine storm results from dysregulation of the innate immune system with an outpouring of proinflammatory cytokines and chemokines, leading to abnormal activation of the adaptive immune pathway. The serious damage caused by coronaviruses such as SARS-COV-2 is due to their infection of both the upper and lower airways, with rapid virus replication and massive inflammatory cell infiltration, producing a huge increase in proinflammatory cytokines and chemokines leading to acute respiratory distress syndrome (125). The initial infection of the airway epithelium leads to rapid viral replication (126, 127), complicated by a virus-induced delayed increase in class 1 interferon (IFNα/β) expression in dendritic cells. that would normally block viral replication and enhance viral clearance by CD8 T cells (128). The delayed expression of class 1 interferon subsequently increases recruitment of proinflammatory cells. Infected airway epithelial cells secrete a number of proinflammatory cytokines/chemokines that further deregulate the innate immune response, and attract the influx of inflammatory cells including neutrophils, monocytes and macrophages, while sensitizing T cells to apoptosis (129). The consequences include a breakdown in the microvascular and alveolar epithelial barrier, resulting in vascular leakage and alveolar edema. The T cell response required for viral clearance is blunted (130), and their role in dampening the cytokine storm is reduced.

A potential role for vitamin D in modulating these pathophysiological aspects of the cytokine storm is noteworthy. Airway epithelia constitutively express both CYP27B1, 1,25$(OH)_2$D, and the vitamin D receptor. Furthermore, pulmonary alveolar macrophages are induced to express both CYP27B1 and the vitamin D receptor by pathogens such as viruses and cytokines released from infected cells. Activation of innate immunity leading to increased local 1,25$(OH)_2$D production has been shown to enhance viral neutralization and clearance while modulating the subsequent proinflammatory response. Whether this sequence of events will be the case for SARS-CoV-2 remains to be seen.

COVID-19 has been associated with cardiovascular sequelae, including myocardial injury, type 1 myocardial infarction, acute coronary syndromes, acute cor pulmonale, cardiomyopathy, arrhythmias, thrombotic complications, and cardiogenic shock (131-133). While no direct causal evidence for a role of vitamin D deficiency in SARS-CoV-2 – related heart disease has been shown, extrapolation of evidence from prior animal and human studies permits speculation of several possible mechanisms. The various risk factors for cardiovascular disease in COVID-19 disease, which are linked to vitamin D deficiency, include hypertension (134), diabetes (135), obesity (136) and chronic kidney disease (137). Vitamin D deficiency may predispose to hypertension by upregulation of the RAAS, and increasing vascular resistance and vasoconstriction (138-140). It is possible that this is further exacerbated by SARS-CoV-2 infection, in which viral binding with cellular entry receptor ACE2 leads to dysregulation of the RAAS in favour of angiotensin-2 (141-142). Activation of the vitamin D receptor also modulates myocardial contractility, likely by regulating calcium flux (144). Several meta-analyses of prospective clinical studies have consistently shown that low 25-OH D serum concentrations indicate an increased risk of overall cardiovascular events and cardiovascular mortality (145-150). Patients with COVID-19 are also at risk for a number of thrombotic complications (151), which may be due to a number of direct and indirect effects of SARS-CoV-2 infection. Several reports have suggested elevated rates of both arterial and venous thrombotic events in patients with COVID-19 (152-156). Moreover, a significant coagulopathy is related to poor prognosis in COVID-19 patients (151, 154). While the mechanisms which lead to these events have yet to be fully elucidated, it is possible that vitamin D levels may be a contributing risk factor. A limited number of clinical reports, antedating the COVID-19 era suggest a link between the vitamin D deficiency and incident thrombotic events, including deep venous thrombosis and cerebrovascular events (157-159). This may be especially true in patients who are critically ill, and require intensive care, among whom low 25-OH D levels have been reported in up to 80% in the pre-COVID-19 era (160-161).

Given the relationship between vitamin D and the RAAS, inflammatory and hemostatic pathways, all of which have been implicated in the development of cardiovascular complications from SARS-CoV-2 infection, further studies evaluating the role of vitamin D in COVID-19-related

cardiovascular and thrombotic events may prove critical to gaining insights into both mechanism and therapeutics.

The link between vitamin D and viral infections arose from the observation of the seasonality of vitamin D with lower levels in the winter and concomitant increases in influenza. Conversely, in summer, serum levels of 25-OH D increase and influenza virtually disappears, except during pandemics. Even in pandemics, most deaths occur during cold months (162). Lower 25-OH D concentrations are associated with a higher risk for infections, especially from the respiratory tract (163). In a retrospective study of 14 108 individuals from the National Health and Nutrition Examination Survey, serum 25-OH D levels <30 ng/mL were associated with 58% higher odds of acute respiratory infections (164-167).

**Vitamin D to COVID-19 infection – clinical data**

In a first, small study (n = 20) of hospitalized COVID-19 patients, vitamin D insufficiency (defined as levels of 25-OH D <30 ng/mL) was present in 75% of the overall cohort and in 85% of those who required ICU care (n = 13) (168). Additionally, an analysis of COVID-19 severity based on survey vitamin D status in Europe suggested that countries with highest rate of vitamin D deficiency are associated with highest rates of infection and death (169). More recently, Ilie et al. observed a significant negative correlation between historical mean 25-OH D concentrations per European country with COVID-19 mortality and number of cases (170). Very recently, Gennari et al. reported lower levels of 25-OH D levels among patients hospitalized with COVID-19 in Italy (171). It is intriguing, that Italy and Spain, which have been heavily affected by COVID-19, are among the European Countries with the highest prevalence of hypovitaminosis D (165). In a sampling of 700 Italian women, 60-80 years old, 25-OH D levels were reported to be lower than 12 ng/mL in 76% (172). Moreover, prevalence of hypovitaminosis D was reported in up to 32% of healthy postmenopausal women in winter and more than 80% in institutionalized individuals (155). In the vast majority of hospitalized elderly Italian subjects, hypovitaminosis D was present with more than half showing severe vitamin D deficiency. Lack of vitamin D also correlated with inflammatory parameters (174). Also a preliminary study from the United States has found a strong correlation of vitamin D deficiency with mortality and other aspects of poorer outcome (175). Marik et al. observed a higher fatality rate for COVID-19 for Northern (>40°N latitude) vs Southern states (6.0% vs 3.5%, P <0.001) in the US (176). In the aggregate, these data suggest a potential deleterious effect of vitamin D deficiency on risk and outcome in COVID-19 disease.

The available clinical data, in brief, are still very preliminary with regard to vitamin D status and COVID-19 disease. Many reports are retrospective, and only associative. Caution is therefore necessary in interpreting the data. Nevertheless, recent publications consistently show a higher prevalence of vitamin D deficiency in patients presenting with severe forms of COVID-19 (177). In addition, putative mechanisms underlying vitamin D's role in immunity and non-skeletal actions, would provide support for the hypothesis advanced that vitamin D deficiency is a risk factor for the disease and/or its adverse outcome. An increasing number of clinical trials are being registered to investigate the effect of vitamin D supplementation or 25-OH D levels on various COVID-19 outcomes (178).

**Conclusion**

For a long time, VD was regarded as an essential factor only in generation (in infancy) and maintenance (primarily in postmenopausal women) of bone mineralization but hardly anything more. However, during the last 10-15 years, many new studies have been published on the extraskeletal effects of VD. One of the best recognized is the production of certain endogenous antimicrobial agents such as cathelicidin and defensins, which provide protection against a wide range of infectious diseases, such as tuberculosis, leprosy and common influenza. Moreover, VD has been shown to be involved in the prevention of certain pathological immune reactions leading to various autoimmune disorders (Type 1 diabetes, colitis, multiple sclerosis, rheumatoid arthritis and graft rejection) and asthma (and other atopic diseases), and even in COPD, which is not regarded as an autoimmune disease. Thus VD, or more precisely VD hypovitaminosis, has tremendous impact on public health. It has to be taken into consideration, that according to epidemiological studies. Majority of the population suffers from VD hypovitaminosis, but for lack of clinical symptoms and lack of interest by doctors the most of these cases are overlooked. One may ask: why worry about the lack of VD exposure if it does not cause any clinical complaints? Especially now, in the era of COVID-19 pandemic, the answer is obvious. The undiagnosed, "hidden" VD hypovitaminosis is involved in the pathogenesis in the above reviewed immunological disorders and even in infectious diseases, however a putative clinical link that between VD and SARS-CoV-2 infection at this time must still be considered hypothetical.

It can be hoped that the public health significance of undiagnosed VD hypovitaminosis will be finally recognized first by the medical community then by society in general. Hopefully more and more people understand that VD deficiency is a risk factor of many diseases affecting broad segments of society. In an ideal scenario, complaint-free people will be regularly screened not only for hypertension, diabetes and various types of cancer but also for VD hypovitaminosis. Epidemiologists might provide more data on that which factors of living conditions and eating habits contribute to VD hypovitaminosis, which has already reached epidemic proportions.

## References

(1) Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 2010; 376(9736):180-188.
(2) Ahn J, Yu K, Stolzenberg-Solomon R, et al. Genome-wide association study of circulating vitamin D levels. Hum Mol Genet 2010; 19(13):2739-2745.
(3) Engelman CD, Meyers KJ, Ziegler JT, et al. Genome-wide association study of vitamin D concentrations in Hispanic Americans: the IRAS family study. J Steroid Biochem. Mol Bio 2010; 122(4):186-192.
(4) Signorello LB, Shi J, Cai Q, et al. Common variation in vitamin D pathway genes predicts circulating 25-hydroxyvitamin D levels among African Americans. PLoS One 2011; 6(12):e28623.
(5) Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 2005; 26(5):662-687.
(6) White JH. Vitamin D signalling, infectious diseases and regulation of innate immunity. Infect Immun 2008; 76(9):3837-3843.

(7) Wang TT, Nestel FP, Bordeau V, et al. Cutting edge: 1,25-dihydroxyvitamin $D_3$ is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004; 173(5):2909-2912.
(8) Bossé Y, Maghni K, Hudson TJ. 1α,25-dihydroxy-vitamin $D_3$ stimulation of bronchial smooth muscle cells induces autocrine, contractility and remodelling processes. Physiol. Genomics 2007; 29:161-168.
(9) Hewison M. Vitamin D and the intracrinology of innate immunity. Molecular and Cellular Endocrinology 2010; 321,103-111.
(10) Hewison M, Freeman L, Hughes SV, et al. Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J. Immunol 2003; 170(11):5382-5390.
(11) Overbergh L, Decallonne B, Waer M, et al. 1α,25-dihydroxyvitamin $D_3$ induces an autoantigen-specific T-helper 1/T-helper 2 immune shift in NOD mice immunized with GAD65 (p524-543). Diabetes 2000; 49(8):1301-1307.
(12) Overbergh L, Decallone B, Waer M. et al. Immune regulation of 25-hydroxyvitamin D-1α-hydroxylase in human monocytic THP-1 cells: mechanisms of interferon-γ-mediated induction. J Endocrinol Metab 2006; 91:3566-3574.
(13) Stoffels K, Overbergh L, Giulietti A, Verlinden L, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin-D3--1α-hydroxylase in human monocytes. J Bone Miner Res 2006; 21(1):37-47.
(14) Jakóbisiak M. Główne komponenty i zasadnicze cechy odpowiedzi immunologicznej. [In.]: Immunologia, 2nd ed.; Wydawnictwo Naukowe PWN; Warsaw, Poland 1995; 28-36.
(15) Bruce D, Ooi JH, Yu S, Cantorna MT. Vitamin D and host resistance to infection? Putting the cart in front of the horse. Exp Biol Med 2010; 235:921-927.
(16) Beard JA.; Bearden A, Striker R. Vitamin D and the anti-viral state. J Clin Virol 2011; 50:194-200.
(17) Bikle DD. Extraskeletal actions of vitamin D. Ann N Y Acad Sci 2016; 1376:29-51.
(18) Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015; 7:4240-4270.
(19) Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. Epidemiol. Infect 2006; 134:1129-1140.
(20) Sundaram ME, Coleman LA. Vitamin D and influenza. Adv Nutr 2012; 3:517-525.
(21) Sadeghi K, Wessner B, Laggner U, et al. vitamin $D_3$ down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. Eur J Immunol 2006; 36(2):361-370.
(22) Szymczak I, Pawliczak R. The active metabolite of vitamin $D_3$ as a potential immunomodulator. Scand J Immunol 2015; 83:83-91.
(23) Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin $D_3$, and the immune system. Am J Clin Nutr 2004/b; 80 (suppl. 6):171S-120S.
(24) Hughes DA, Norton R. Vitamin D and respiratory health. Clin Exp Immunol 2009; 158(1):20-25.
(25) Nizet V, Ohtake T, Lauth X et al. Innate antimicrobial peptide protects the skin from invasive bacterial infection. Nature 2001; 414(6862):454-457.
(26) Saiman L, Tabibi S, Starner TD, et al. Cathelicidin peptides multiply antibiotic-resistant pathogens from patients with cystic fibrosis. Antimicrob. Agents Chemother 2001; 45:2838-2844.
(27) Zhang L, Yu W, He T, et al. Contribution of human α-defensin 1, 2, and 3 to the anti-HIV-1 activity of CD8 antiviral factor. Science 2002; 298(5595):995-1000.
(28) Ganz T. Defensins: antimicrobial peptides of innate immunity. Nat Rev Immunol 2003; 3(9):710-720.
(29) Menzies BE, Kenoyer A. Signal transduction and nuclear responses in Staphylococcus aureus-induced expression of human β-defensin 3 in skin keratinocytes. Infect Immunol 2006; 74(12):6847-6854.
(30) Herr C, Shaykhiev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory diseases. Expert Opin Biol Ther 2007; 7 (9):1449-1461.
(31) Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). J Cyst Fibros 2007; 6(6):403-410.
(32) Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 2007; 179(4):2060-2063.
(33) Martineau AR, Wilkinson KA, Newton SM, et al. IFNγ – and TNF – independent vitamin D – inducible human suppression of mycobacteria: the role of cathelicidin LL-37. J Immunol 2007; 178:7190-7198.
(34) Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311:1770-1773.
(35) Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V, Gombart AF, Borregaard N, Modlin RL, Hewison M. Vitamin D-directed rheostatic regulation of monocyte antibacterial responses. Journal of Immunology 2009; 182:4289-4295.
(36) Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, Lee ZW, Lee SH, Kim JM, Jo EK. Vitamin $D_3$ induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host and Microbe 2009; 6:231-243.
(37) Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up regulated in myeloid cells by 1,25-dihydroxyvitamin $D_3$. FASEB Journal 2005; 19:1067-1077.
(38) Kim J, Yang YL, Jang SH, Jang YS. Human beta-defensin 2 plays a regulatory role in innate antiviral immunity and is capable of potentiating the induction of antigen-specific immunity. Virology Journal 2018; 15, 124.
(39) Gough ME, Graviss EA, May EE. The dynamic immunomodulatory effects of vitamin $D_3$ during Mycobacterium infection. Innate Immunity 2017; 23, 506-523.
(40) Hubel E, Kiefer T, Weber J, Mettang T, Kuhlmann U. In vivo effect of 1,25-dihydroxyvitamin $D_3$ on phagocyte function in hemodialysis patients. Kidney International 1991; 40, 927-933.
(41) Subramanian K, Bergman P, Henriques-Normark B. Vitamin D promotes pneumococcal killing and modulates inflammatory responses in primary human neutrophils. Journal of Innate Immunity 2017; 9, 375-386.
(42) 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.
(43) Shi YY, Liu TJ, Fu JH, Xu W, Wu LL, Hou AN, Zue XD. Vitamin D/VDR signaling attenuates lipopolysaccharideinduced acute lung injury by maintaining the integrity of the pulmonary epithelial barrier. Molecular Medicine Reports 2016; 13, 1186-1194.
(44) Schrumpf JA, van Sterkenburg MAJA, Verhoosel RM et al. Interleukin 13 exposure enhances vitamin D-mediated expression of the human cathelicidin antimicrobial peptide 18/LL-37 in bronchial epithelial cells. Infection and Immunity 2012; 80(12):4485-4494.

(45) van der Does AM, Bergman P, Agerberth B, Lindbom L. Induction of the human cathelicidin LL-37 as a novel treatment against bacterial infections. Journal of Leukocyte Biology 2012; 92(4)735-742.
(46) Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015; 7(6):4240-4270.
(47) Chun RF, Liu PT, Modlin RL, et al Impact of vitamin D on immune function: Lessons learned from genome-wide analysis. Front Physiol 2014; 5, 1-15.
(48) Adler HS, Steinbrink K. Tolerogenic dendritic cells in health and disease: friend and foe. Eur J Dermatol 2007; 17(6):476-491.
(49) Massoud AH, Guay J, Shalaby KH, et al. Intravenous immunoglobulin attenuates airway inflammation through induction of forkhead box protein 3-positive regulatory T cells. J Allergy Clin Immunol 2012; 129(6):1656-1665.e3.
(50) Van der Aar AM, Sibiryak DS, Bakdash G et al. Vitamin $D_3$ targets epidermal and dermal dendritic cells for induction of distinct regulatory T cells. J. Allergy Clin Immunol 2011; 127(6):1532-1540.
(51) Fu S, Zhang N, Yopp AC, et al. TGF-β induces $FOXp3^+$ T regulatory cells from $CD4^+$ $CD25^+$ precursors. Am J Transplant 2004; 4(10):1614-1627.
(52) Lyakh LA, Sanford M, Chekol S, et al. TGF-β and vitamin $D_3$ utilize distinct pathways to suppress IL-12 production and modulate rapid differentiation of human monocytes into $CD83^+$ dendritic cells. J Immunol 2005; 174(4):2061-2070.
(53) Roncarolo MG, Gregori S, Battaglia M, et al. Interleukin-10 secreting type-1 regulatory T cells in rodents and humans. Immunol Rev 2006; 212:28-50.
(54) Boks MA, Kager-Groenland JR, Haasjes MS, et al. IL-10-generated tolerogenic dendritic cells are optimal for functional regulatory T cell induction – a comparative study of human clinical-applicable DC. Clin Immunol 2012; 142(3):332-342.
(55) Adorini L. Tolerogenic dendritic cells induced by vitamin D receptor ligand enhance regulatory T cells inhibiting autoimmune diabetes. Ann N Y Acad Sci 20003; 987(Apr):258-261.
(56) Adorini L, Penna G. Induction of tolerogenic dendritic cells by vitamin D receptor agonists. Handb Exp Pharmacol 2009; (188):251-273.
(57) Griffin MD, Lutz WH, Phan VA, et al. Potent inhibition of cell differentiation and maturation by vitamin D analogs. Biochem Biophys Res Commun 2000; 270(3):701-708.
(58) Van Etten E, Mathieu C. Immunoregulation by 1,25 dihydroxyvitamin $D_3$: basic concepts. J Steroid Biochem Mol Biol 2005; 97(1-2):93-101.
(59) Eagar TN, Tompkins SM, Miller SD. Helper T-cell subsets and control of the inflammatory response. [In.]: Clinical Immunology. Rich RR, Fleisher TA, Shearer WR et al. [Eds.]. Mosby, London, UK. Section 2, Chapter 16, 16.1-16.12 (2001).
(60) O'Shea JJ, Frucht DM, Duckett CS. Cytokines and cytokine receptors. [In.]: Clinical Immunology. Rich RR, Fleisher TA, Shearer WR et al. [Eds.]. Mosby, London, UK. Section 1, Chapter 12, 12.1-12.22 (2001).
(61) Jeffery LE, Burke RF, Mura M, et al. 1,25-dihydxroxyvitamin $D_3$ and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J Immunol 2009; 183(9):5458-5467.
(62) Bluestone JA. Is CTLA-4 a master switch for peripheral T cell tolerance? J Immunol 1997; 158(5):1989-1993.
(63) Takahashi T, Tagami T, Yamazaki S et al. Immunological self-tolerance maintained by $C25(^+)CD4(^+)$ regulatory T cells constitutively expressing cytotoxic T-lymphocyte associated antigen 4. J Exp Med 2000; 192(2):303-310.
(64) Imazeki I, Matsuzaki J, Tsuji K, Nishimura T. Immunomodulating effect of vitamin $D_3$ derivatives on type-1 cellular immunity. Biomed Res 2006; 27(1):1-9.
(65) Barrat FJ, Cua DJ, Boonstra A, et al. In vitro generation of interleukin-10 producing regulatory $CD4(^+)$ T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (TH1)- and TH2-inducing cytokines. J Exp Med 2002; 195(5):603-616.
(66) Thornton AM, Shevach EM. $CD4^+CD25^+$ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin-2 production. J Exp Med 1998; 188(2):287-290.
(67) Joshi S, Pantalena LC, Liu XK et al. 1,25-dihydoxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin 17A. Mol Cell Biol 2011; 31(17):3653-3669.
(68) Wang KS, Frank DA, Ritz J. Interleukin-2 enhances the response of natural killer cells to interleukin-12 through up-regulation of the interleukin-12 receptor and STAT4. Blood 2000; 95(10):3183-3190.
(69) Boonstra A, Barrat FJ, Crain C, et al. α,25-dihydroxyvitamin $D_3$ has a direct effect on naive $CD4(^+)$ T cells to enhance the development of Th2 cells. J Immunol 2001; 167(1):4974-4980.
(70) Thornton AM, Shevach EM. $CD4^+CD25^+$ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. J Exp Med 1998; 188(2):287-296.
(71) Xia JB, Wang CZ, Ma JX, An XJ. Immunoregulatory role of 1, 25-dihydroxyvitamin D(3)-treated dendritic cells in allergic airway inflammation. Zhonghua Yi Xue Za Zhi 2009; 89(8):514-518.
(72) Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003; 299(5609):1057-1061.
(73) Roncarolo M-G, Levings MK. The role of different subsets of T regulatory cells in controlling autoimmunity. Curr Opin Immunol 2000; 12(6):676-683.
(74) Roncarolo M-G, Levings MK, Traversari C. Differentiation of T regulatory cells by immature dendritic cells. J Exp Med 2001; 193(2):F5-F9.
(75) Urry Z, Xystrakis E, Richards DF et al. Ligation of TLR9 induced on human IL-10-secreting Tregs by 1α,25-dihydroxyvitamin $D_3$ abrogates regulatory functions. J Clin Invest 2009; 119(2):387-398.
(76) Saggese G, Federico G, Balestri M, Toniolo A. Calcitriol inhibits the PHA-induced production of IL-2 and IFN-gamma and the proliferation of human peripheral blood leukocytes while enhancing the surface expression of HLA class II molecules. J Endocrinol Invest 1989; 12(5):329-335.
(77) Alroy I, Towers TL, Freedman LP. Transcriptional repression of the interleukin2-gene by vitamin $D_3$: direct inhibition of NFATp/AP-1 complex formation by nuclear hormone receptor. Mol Cell Biol 1995; 15(10):5789-5799.
(78) Matilainen JM, Räsänen A, Gynther P, Väisänen S. The genes encoding cytokines IL-2, IL-12 and IL-12B are primary $1\alpha,25(OH)_2D_3$ target genes. J Steroid Biochem Mol Biol 2010; 121(1-2):142-145.
(79) Takeuchi A, Reddy GS, Kobayashi T. Nuclear factor of activated T cells (NFAT) as a molecular target for 1α, 25-dihydroxyvitamin $D_3$-mediated effects. J Immunol 1998; 160(1):209-218.
(80) Lemire JM, Adams JS, Kermani-Arab V et al. 1,25-dihydoxyvitamin $D_3$ suppresses human T helper/induces lymphocyte activity in vitro. J Immunol 1985; 134(5):3022-3025.
(81) Cantorna MT, Zhao J, Yang L. Vitamin D, invariant natural killer T-cells and experimental autoimmune disease. Proc Nutr Soc 2011a; 14, 1-5.

(82) Yu S, Zhao J, Cantorna MT. Invariant NKT cell defects in vitamin D receptor knockout mice prevents experimental lung inflammation. J Immunol 2011; 187(9):4907-4912.
(83) Bouillon R, Carmeliet G, Verlinden L, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 2008; 29(6):726-776.
(84) Cantorna MT, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin $D_3$ reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc Natl Acad Sci USA 1996; 93(15):7861-7864.
(85) Nataf S, Garcion E, Darcy F, et al. 1,25 dihydroxyvitamin $D_3$ exerts regional effects in the central nervous system during experimental allergic encephalomyelitis. J Neuropathol Exp Neurol 1996; 55(8):904-914.
(86) Ho SL, Alappat L, Awad AB. Vitamin D and multiple sclerosis. Crit Rev Food Sci Nutr 2012; 52(11):980-987.
(87) Brown SJ. The role of vitamin D in multiple sclerosis. Ann Pharmacother 2006; 40(6):1158-1161.
(88) Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006; 296(23):2832-2838.
(89) Froicu M, Weaver CV, Wynn TA et al. A crucial role for the vitamin D receptor in experimental bowel diseases. Mol Endocrinol 2003; 17(12):2386-2392.
(90) Lim WC, Hanauer SB, Li YC. Mechanism of disease: vitamin D and inflammatory bowel disease. Natl Clin Gastroenterol Hepatol 2005; 2(7):308-315.
(91) Park SY, Gupta D, Kim CH, Dziarski R. Differential effects of peptidoglycan recognition proteins on experimental atopic and contact dermatitis mediated by Treg and Th17 cells. PLoS ONE 2011; 6(9):e24961.
(92) Colin EM, Asmawidjaja PS, van Hamburg JP et al. 1,25-dihydroxyvitamin $D_3$ modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis. Arthritis Rheum 2011; 62(1):132-142.
(93) Hullett DA, Cantorna MT, Redaelli C et al. Prolongation of allograft survival by 1,25-dihydroxyvitamin $D_3$. Transplantation 1998; 66(7):824-828.
(94) Adorini L. 1,25-dihydroxyvitamin $D_3$ analogs as potential therapies in transplantation. Curr Opin Investig Drugs 2002; 3(10):1458-1463.
(95) Zhang AB, Zheng SS, Jia CK, Wang Y. Effect of 1,25-dihydroxyvitamin $D_3$ on preventing allograft from acute rejection following rat orthotopic liver transplantation. World J Gastroenterol 2003; 9(5):1067-1071.
(96) Hullett DA, Laeseke PF, Malin G, Nessel R, Sollinger HW, Becker BN. Prevention of chronic allograft nephropathy with vitamin D. Transpl Int 2005; 18(10):1175-1186.
(97) Zittermann A, Tenderich G, Koerfer R. Vitamin D and the adaptive immune system with special emphasis to allergic reactions and allograft rejection. Inflamm. Allergy Drug Targets 2009; 8(2):161-168.
(98) Bitetto D, Fabris C, Falleti E et al. Vitamin D and the risk of acute allograft rejection following human liver transplantation. Liver Int 2010; 30 (3):417-444.
(99) Stein EM, Shane E. Vitamin D in organ transplantation. Osteoporos Int 2011; 22 (7):2107-2118.
(100) Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infectious Diseases 2020; 20(5):533-534.
(101) Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine 2020; 382; 1708-1720.
(102) Shi S, Qin M, Shen B ,et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiology 2020; 25; 802-810.
(103) Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054-1062.
(104) Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X & Du C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Medicine 2020; 180, 1-11.
(105) Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368, m1091.
(106) Petrilli CM, Jones SA, Yang J, at al. Factors associated with hospital admission and crticial illness among 5279 people with coronavirus disease 2019 in New York City: a prospective cohort study. BMJ 2020; 369, m1966.
(107) Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? Lancet: Diabetes and Endocrinology 2020; 8:570
(108) Marazuela M, Giustina A,Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Reviews in Endocrine and Metabolic Disorders 2020 In press.
(109) Hastie CE, Mackay DF, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2020; 14:561-565.
(110) Barlow PG, Svoboda P, Mackellar A, at al. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS ONE 201; 6e25333.
(111) Campbell GR, Spector SA. Autophagy induction by vitamin D inhibits both Mycobacterium tuberculosis and human immunodeficiency virus type 1. Autophagy 2012; 8(10):1523-1525.
(112) Campbell GR, Spector SA. Vitamin D inhibits human immunodeficiency virus type 1 and Mycobacterium tuberculosis infection in macrophages through the induction of autophagy. PLoS Pathogens 2012; 8(5):e1002689.
(113) Mao J, Lin E, He L, et al. Autophagy and viral infection. Advances in Experimental Medicine and Biology 2019; 1209:55-78.
(114) Mushegian AA. Autophagy and vitamin D. Science Signaling 2017; 10; eaan2526.
(115) Shin DM, Yuk JM, Lee HM, et al. Mycobacterial lipoprotein activates autophagy via TLR2/1/CD14 and a functional vitamin D receptor signalling. Cellular Microbiology 2010; 121:648-1665.
(116) Jang W, Kim HJ, Li H, et al. 1,25-Dyhydroxyvitamin D(3) attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy. Biochemical and Biophysical Research Communications 2014; 451:142-147.
(117) Wang J. Beclin 1 bridges autophagy, apoptosis and differentiation. Autophagy 2008; 4:947-948.
(118) Uberti F, Lattuada D, Morsanuto V, et al. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. Journal of Clinical Endocrinology and Metabolism 2014; 99:1367-1374.
(119) Campbell GR, Spector SA. Hormonally active vitamin $D_3$ (1alpha,25 dihydroxycholecalciferol) triggers autophagy in human macrophages that inhibits HIV-1 infection. Journal of Biological Chemistry 2011; 286:18890-18902.
(120) Campbell GR, Spector SA. Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response that inhibits human immunodeficiency virus type 1. PLoS Pathogens 2012; 8 e1003017.
(121) Khare D, Godbole NM, Pawar SD, et al. Calcitriol [$1,25(OH)_2D_3$] pre- and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung

A549 epithelial cells. European Journal of Nutrition 2013; 52:1405-1415.
(122) Tian G, Liang X, Chen D, et al. Vitamin $D_3$ supplementation alleviates rotavirus infection in pigs and IPEC-J2 cells via regulating the autophagy signaling pathway. Journal of Steroid Biochemistry and Molecular Biology 2016; 163:157-163.
(123) Abdel-Mohsen MA, El Braky A, Ghazal AAE, Shamseya MM. Autophagy, apoptosis, vitamin D, and vitamin D receptor in hepatocellular carcinoma associated with hepatitis C virus. Medicine 2018; 97:e0172.
(124) Teymoori-Rad M, Shokri F, Salimi V, Marashi SM. The interplay between vitamin D and viral infections. Reviews in Medical Virology 2019; 29:e2032.
(125) Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Seminars in Immunopathology 2017; 39:529-539.
(126) Chu CM, Poon LL, Cheng VC, et al. Initial viral load and the outcomes of SARS. Canadian Medical Association Journal 2004; 171:1349-1352.
(127) Oh MD, Park WB, Choe PG et al. Viral load kinetics of MERS coronavirus infection. New England Journal of Medicine 2016; 375:1303-1305.
(128) Kohlmeier JE, Cookenham T, Roberts AD et al. Type I interferons regulate cytolytic activity of memory CD8(+) T cells in the lung airways during respiratory virus challenge. Immunity 2010; 33:96-105.
(129) Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated Type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host and Microbe 2016; 19:181-193.
(130) Zhao J, Zhao J, Perlman S. T-cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. Journal of Virology 2010; 84:9318-9325.
(131) Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. Journal of the American College of Cardiology 2020, 75:2352-2371.
(132) Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation 2020; 141:1648-1655.
(133) Bangalore S, Sharma A, Slotwiner A. et al. ST-segment elevation in patients with COVID-19 – a case series. New England Journal of Medicine 2020; 382:2478-2480.
(134) Kunutsor SK, Apekey TA, Steur M. Vitamin D and Risk of Future Hypertension: Meta Analysis of 283, 537 Participants. Springer, 2013.
(135) Song Y, Wang L, Pittas AG et al. Blood 25 hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 2013; 36:1422-1428.
(136) Pereira-Santos M, Costa PR, Assis AM, et al. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obesity Reviews 2015; 16:341-349
(137) Dusso AS, Tokumoto M. Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: a downward spiral in kidney disease. Kidney International 2011. 79:715-729. 103.
(138) Yuan W, Pan W, Kong J et al. 1,25-Dihydroxyvitamin $D_3$ suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. Journal of Biological Chemistry 2007; 282:29821-29830.
(139) Li YC. Molecular mechanism of vitamin D in the cardiovascular system. Journal of Investigative Medicine 2011; 59:868-871.
(140) Chen S, Sun Y, Agrawal DK. Vitamin D deficiency and essential hypertension. Journal of the American Society of Hypertension 2015; 9:885-901.
(141) Ye M, Wysocki J, William J, et al. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. Journal of the American Society of Nephrology 2006; 17:3067-3075.
(142) Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacology and Therapeutics 2010; 128:119-128.
(143) Strawn WB, Ferrario CM, Tallant EA. Angiotensin-(1-7) reduces smooth muscle growth after vascular injury. Hypertension 1999; 33:207-211.
(144) Pilz S, Tomaschitz A, Drechsler C et al. Vitamin D deficiency and myocardial diseases. Molecular Nutrition and Food Research 2010; 54:1103-1113.
(145) Wang L, Song Y, Manson JE et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circulation: Cardiovascular Quality and Outcomes 2012; 5:819-829.
(146) Brøndum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-Hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death: population based study and meta-analyses of 18 and 17 studies. Arteriosclerosis, Thrombosis, and Vascular Biology 2012; 32:2794-2802.
(147) Sokol SI, Tsang P, Aggarwal V, Melamed ML, Srinivas VS. Vitamin D status and risk of cardiovascular events: lessons learned via systematic review and meta-analysis. Cardiology in Review 2011; 19:192-201.
(148) Pittas AG, Chung M, Trikalinos T, et al. Systematic review: vitamin D and cardiometabolic outcomes. Annals of Internal Medicine 2010; 152:307-314.
(149) Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014; 348:g2035.
(150) Tomson J, Emberson J, Hill M, et al. Vitamin D and risk of death from vascular and non-vascular causes in the Whitehall study and meta-analyses of 12 000 deaths. European Heart Journal 2013; 34:1365-1374.
(151) Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow up. Journal of the American College of Cardiology 2020; 75:2950-2973.
(152) Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research 2020; 191:145-147.
(153) Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of Thrombosis and Haemostasis 2020; 18:1094-1099.
(154) Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis 2020; 18:844-847.
(155) Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation 2020; 142:184-186.
(156) Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurology 2020; 77:1-9.
(157) Entezari-Maleki T, Talasaz AH, Salarifar M, et al. Plasma vitamin D status and its correlation with risk factors of thrombosis, P-selectin and hs-CRP level in patients with venous

thromboembolism; the first Study of Iranian Population. Iranian Journal of Pharmaceutical Research 2014; 13:319-327.
(158) Wu WX, He DR. Low vitamin D levels are associated with the development of deep venous thromboembolic events in patients with ischemic stroke. Clinical and Applied Thrombosis/Hemostasis 2018; 24:69S-75S.
(159) Khademvatani K, Seyyed-Mohammadzad MH, Akbari M, et al. The relationship between vitamin D status and idiopathic lower-extremity deep vein thrombosis. International Journal of General Medicine 2014; 7:303-309.
(160) Amrein K, Schnedl C, Berghold A, Pieber TR, Dobnig H. Correction of vitamin D deficiency in critically ill patients – VITdAL@ICU study protocol of a double-blind, placebo controlled randomized clinical trial. BMC Endocrine Disorders 2012; 12;27.
(161) Azim A, Ahmed A, Yadav S, et al. Prevalence of vitamin D deficiency in critically ill patients and its influence on outcome experience from a tertiary care centre in North India (an observational study). Journal of Intensive Care 2013; 1:14.
(162) Cannell JJ, Vieth R, Umhau JC, Holick MF, et al. Epidemic influenza and vitamin D. Epidemiology and Infection 2006; 134:1129-1140.
(163) Mathyssen C, Gayan-Ramirez G, Bouillon R, Janssens W. Vitamin D supplementation in respiratory diseases: evidence from randomized controlled trials. Polish Archives of Internal Medicine 2017; 127:775-784.
(164) Science M, Maguire JL, Russell ML, et al. Low serum 25 hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. Clinical Infectious Diseases 2013; 57:392-397.
(165) Dancer RC, Parekh D, Lax S, et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 2015; 70:617-624.
(166) Monlezun DJ, Bittner EA, Christopher KB, Camargo CA, Quraishi SA. Vitamin D status and acute respiratory infection: cross sectional results from the United States National/Health and Nutrition Examination Survey, 2001-2006. Nutrients 2015; 7:1933-1944.
(167) Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. Health Technology Assessment 2019; 23:1-44.
(168) Lau FH, Majumder R, Torabi R et al. Vitamin D insufficiency is prevalent in severe COVID-19. medRxiv 2020. https://doi.org/101101/2020.04.24.20075838.
(169) Lanham-New SA, Webb AR, Cashman KD, et al. Vitamin D and SARS-CoV-2 virus/COVID-019 disease. BMJ Nutrition, Prevention and Health 2020; 3:106-110.
(170) Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clinical and Experimental Research 2020; 32:1195-1198.
(171) Gennari L, Campi I, Merlotti D, et al. Vitamin D deficiency is independently associated with COVID-19 severity and mortality. ASBMR Annual Meeting, 2020.
(172) Isaia G, Giorgino R, Rini GB, et al. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. Osteoporosis International 2003; 14:577-582.
(173) Romagnoli E, Caravella P, Scarnecchia L, Martinez P, Minisola S. Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients. British Journal of Nutrition 1999; 81:133-137.
(174) Boccardi V, Lapenna M, Gaggi L et al. Hypovitaminosis D: a disease marker in hospitalized very old persons at risk of malnutrition. Nutrients 2019; 11:128.
(175) Daneshkhah A, Agrawal V, Eshein A, et al. The possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. medRxiv 2020.04.08.20058578. https://doi.org/10.1101/2020.04.08.20058578.
(176) Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? Medicine in Drug Discovery 2020; 6:100041.
(177) Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12:988.
(178) Gupta R, Hussain A, Misra A. Diabetes and COVID-19: evidence, current status and unanswered research questions. European Journal of Clinical Nutrition 2020; 74:864-870.