Vitamin D, infections and immunity

Witamina D, zakażenia i odporność

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- vitamin D
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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 katelidyna i defensyny. VD zmniejsza prezentację antigenów przez komórki dendrytyczne, hamuje polaryzację komórek Th0 do komórek Th1 lub–2 i ogranicza produkcję cytokin zapalnych, 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.

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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 D3 (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. 1a-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 in 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 (hNPP1-3) 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).

VD 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 phagocytic 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 naïve 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-10, 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 autoimmunity 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 naïve 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 inhibition 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 naïve 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 hepatitis C (123). In considering the effects of vitamin D on autophagy, it is 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 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 CД8 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)2D, 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)2D 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 but not pre-existing thrombotic events including deep vein 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 mortality 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, vitamin D was regarded as an essential factor only in generation (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 vitamin D. One of the best recognized is the production of certain endogenous antimicrobial agents such as cathelodium and defensins, which provide protection against a wide range of infectious diseases, such as tuberculosis, leprosy and common influenza. Moreover, vitamin D 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 vitamin D, or more precisely vitamin D 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 vitamin D 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 vitamin D 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” vitamin D hypovitaminosis is involved in the pathogenesis in the above reviewed immunological disorders and even in infectious diseases, however a putative clinical link that between vitamin D and SARS-CoV-2 infection at this time must still be considered hypothetical.

It can be hoped that the public health significance of undiagnosed vitamin D hypovitaminosis will be finally recognized first by the medical community then by society in general. Hopefully more and more people understand that vitamin D 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 vitamin D hypovitaminosis. Epidemiologists might provide more data on that which factors of living conditions and eating habits contribute to vitamin D hypovitaminosis, which has already reached epidemic proportions.

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