



Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship?

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1. Introduction

Infections of the respiratory tract are more frequent in the winter months and especially in the northern latitudes than they are in summer [1]. This obviously also applies to the COVID-19 infectious disease that briefly spread all over the world in the winter months and became a pandemic [2,3]. A common feature of the winter months and the inhabitants of all countries north of the 42nd parallel is a hypovitaminosis D that frequently occurs during this period [4]. In addition during cold temperature the virus will be more easily transmitted. This raises the question of whether an inadequate vitamin D supply has an influence on the progression and severity of COVID-19 disease.

A low vitamin D status, measured as the plasma level of the transport form of vitamin D, 25(OH)D, is widespread worldwide and is mainly found in regions of northern latitudes, but also in southern countries [5]. In Europe, vitamin D deficiency is widely prevalent during the winter months and affects mainly elderly people and migrants. In Scandinavia only 5% of the population is affected by a low vitamin D status, in Germany, France and Italy more than 25%, particularly older people e.g. in Austria up to 90% of senior citizens [6,7]. In Scandinavian countries, the low incidence of vitamin D deficiency may be due to the traditional consumption of cod liver oil rich in vitamin D and A or to genetic factors resulting in higher synthesis of vitamin D in the epidermal layer [8]. Taken together, low vitamin D status is common in Europe with the exception of the Scandinavian countries. The calculated COVID-19 mortality rate from 12 European countries shows a significant ($P = .046$) inverse correlation with the mean 25(OH)D plasma concentration [9].

This raises the question whether insufficient vitamin D supply has an influence on the course of COVID-19 disease? An analysis of the distribution of Covid-19 infections showed a correlation between geographical location (30–50° N+), mean temperature between 5–11 °C and low humidity [10]. In a retrospective cohort study (1382 hospitalized patients) 326 died, Among them 70.6% were black patients. However, black race was not independently associated with higher mortality [11]. An excess mortality (2 to sixfold) has been described in African-Americans with average latitudes of their state of residence in higher latitudes (> 40) [12]. The mortality of COVID-19 (cases/ million population) shows a clear dependence on latitude. Below latitude

35, mortality decreases markedly [13]. Indeed, there are exceptions e.g. Brazil (tenfold higher than all other Latin American countries – except Mexico), however, the management of the pandemic may increase infection risk.

1.1. Vitamin D effects

The skeletal and extra skeletal effects of vitamin D have recently been described in an extensive review [14]. Vitamin D exerts a genomic and non-genomic effect on gene expression. The genomic effect is mediated by the nuclear vitamin D receptor (VDR), which acts as a ligand activated transcription factor. The active form 1,25(OH)₂D binds to the VDR and in most cases heterodimerizes with the retinoid X receptor (RXR), whose ligand is one of the active metabolites of vitamin A, 9-cis retinoic acid. The interaction of this complex with the vitamin D responsive element can regulate the expression of target genes either positively or negatively [15]. The non-genomic effects involve the activation of a variety of signaling molecules that interact with Vitamin D responsive element (VDRE) in the promoter regions of vitamin D dependent genes [16]. Vitamins A and D are also of particular importance for the barrier function of mucous membranes in the respiratory tract [17,18].

1.2. Vitamin D and immune system

Vitamin D plays an essential role in the immune system [19]. Vitamin D interferes with the majority of the immune system cells such as macrophages, B and T lymphocytes, neutrophils and dendritic cells, which express VDR (for details [20] and Fig. 3). Cathelicidin, a peptide formed by vitamin D stimulated expression, has shown antimicrobial activity against bacteria, fungi and enveloped viruses, such as corona viruses [21,22]. Furthermore Vitamin D inhibits the production of pro-inflammatory cytokines and increases the production of anti-inflammatory cytokines [23].

The active metabolite of vitamin D in macrophages and dendritic cells, derived from the precursor 25(OH)D, leads to the activation of VDR, which, after RXR heterodimerization, results in the expression of various proteins of the innate and adaptive immune system (Treg cells, cytokines, defensins, pattern recognition receptors etc.) [24]. Vitamin D

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exerts opposite effects on the adaptive (inhibition) and innate (promotion) immunosystem. This correlates with an anti-inflammatory response and balances the immune response [25].

The active metabolite of vitamin D, 1,25(OH)₂D₃ can be formed in T and B lymphocytes and inhibits T cell proliferation and activation [26]. This way, vitamin D may suppress T-cell mediated inflammation and stimulate Treg cells proliferation, by increasing IL-10 formation in DC cells, and thus enhance their suppressive effect [27,28].

1.3. Food sources

There are only few dietary sources of vitamin D (cod liver oil, fat fish) that could satisfy the recommended daily allowance (15–20 µg/day for adults). To reach such amount besides availability of dietary sources, vitamin D skin synthesis, which contributes to 80% in healthy individuals up to the age of 65, is important.

With the exception of mushrooms there are no plant sources of vitamin D. In particular wild mushrooms, which are grown in light. Sun-dried but not fresh mushrooms can contain between 7 and 25 µg/100 g of vitamin D₂ [29], which is an important source [30] with a good shelf life [31] and comparable bioavailability to vitamin D₃ [32]. Vitamin D status can be significantly improved by fortified foods, as was shown in a meta-analysis [33].

1.4. Vitamin D deficiency

Insufficient levels of vitamin D are caused by two main physiological causes: Low UVB exposure, especially in northern regions during the winter season [34] and in case of strong pigmentation, as well as decreased vitamin synthesis in the skin with aging [35]. In addition a poor diet, low in fish and fortified food (if available) are the major reason for deficiency in old age and people living in poverty. Major risk groups [36], besides pregnant women and children under 5, include elderly, over 65 years, those with little or no sun exposure (full body coverage, little contact with the outside world) as well as people with dark skin, especially in Europe and the USA.

The vitamin D deficiency is a worldwide problem, which is not only observed in the northern countries, but increasingly also in the south. While in Europe, for example, deficits (< 30 nmol) are between 20 and 60% in all age groups, in Asia the figure for children is 61% (Pakistan, India) and 86% (Iran) [37,38].

Particularly critical is the number of migrants from Southern countries with insufficient vitamin D status (< 25 nmol/L) [39]: e.g. Netherlands 51%, Germany 44% (in summer), UK 31% (end of summer) and 34% (autumn). In India, the number of adults with values < 25 nmol/L ranges from 20% to 96% depending on the region.

The half-life of 25(OH)D₃ is about 15 days and that of 25(OH)D₂ is between 13 and 15 days, due to the weaker affinity to the vitamin D binding protein [40]. Consequently, longer periods of time indoor, e.g. in care homes or longer time in quarantine, pose risk for developing vitamin D deficiency.

1.5. Risk factors for severe courses of COVID-19

Older age and co-morbidities are linked to an insufficient vitamin D supply. Over 60 years of age, a reduction in the synthesis of vitamin D in the skin becomes apparent, which further increases getting older [41]. The precursor of vitamin D, 7-dehydrocholesterol in the skin declines about 50% from age 20 to 80 [42], and the elevation of cholecalciferol levels in serum following UVB radiation of the skin shows more than a 4-fold difference in individuals aged 62–80 yrs. compared with controls (20–30 yrs) [43]. This explains the high number of older individuals with an inadequate vitamin D status.

Based on a meta-analysis including 30 studies with 53,000 COVID-19 patients, co-morbidities are risk factors for disease severity:

| Risk factor | Odds ratio | 95% CI |
|-------------------------|------------|--------------|
| Old age > 50 yrs | 2.61 | 2.29–2.98 |
| Male | 1.38 | 1.195–1.521 |
| Smoking | 1.734 | 1.146–2.626 |
| Any co-morbidity | 2.635 | 2.098–3.309 |
| Chronic kidney disease | 6.017 | 2.192–16.514 |
| COPD | 5.323 | 2.613–10.847 |
| Cerebrovascular disease | 3.219 | 1.486–6.972 |

Independent prognostic factors for COVID-19 related death:

| Risk factor | Relative risk | 95% CI |
|--------------|---------------|------------|
| Old age > 60 | 9.45 | 8.09–11.04 |
| CVD | 6.75 | 5.40–8.43 |
| Hypertension | 4.48 | 3.69–5.45 |
| Diabetes | 4.43 | 3.49–5.61 |

Co-morbidities and old age show a relationship with Renin-Angiotensin-Aldosterone-System (RAS), vitamin D status and COVID-19 infection.

1.6. The renin-angiotensin-system (RAS)

RAS plays an important role in maintaining vascular resistance and extracellular fluid homeostasis. Fig. 1 summarizes the essential steps of this system.

Mainly in the juxtaglomerular apparatus of the kidney, but also in other tissues and cells, renin is formed, which cleaves the angiotensinogen secreted from the liver very selectively to the inactive form angiotensin I (Ang I). This decapeptide is then cleaved by a further protease the angiotensin-converting-enzyme (ACE) on the surface of the endothelial cells to the active angiotensin II (Ang II), which can bind to two different receptors AT1R or AT2R. Synthesis and secretion of renin in the kidney, as rate limiting enzyme of RAS, is stimulated by fluid volume, reduction of the perfusion pressure or salt concentration and by the sympathetic nervous system activity.

Renin synthesis and secretion is inhibited with increasing Ang II via an AT1R mediated effect and stimulated with decreasing Ang II [44]. The stimulating effect on renin synthesis and secretion due to either low levels of Ang II or Ang II converting inhibitors (ACEI) or Ang II receptor blockers (ARB) is mediated through ligands that activate cAMP/PKA (Protein Kinase A) pathways (e.g. catecholamines, prostaglandins and nitric oxide) [45,46].

Ang II leads to the release of catecholamines and vasoconstriction. Via AT1R, Ang II increases aldosterone release and sodium reabsorption. Furthermore, binding to AT1R has pro-inflammatory and pro-oxidative effects and inhibits the action of insulin in endothelial and muscle cells. The latter can lead to a decrease in NO production in endothelial cells and thus will further increase vasoconstriction [47].

With the discovery of ACE2, a novel homologue of ACE, a transmembrane metallopeptidase with an extracellular ectodomain, the understanding of RAS manifold regulatory function was deepened (Review [48]). ACE2, a monocarboxypeptidase has been shown to cleave Ang I to Ang 1–9, and Ang II to Ang 1–7. This degradation can weaken the effect of Ang II at AT1R and thus counteract the pathological changes. While Ang 1–9 exerts a cardioprotective effect via AT2R [49], Ang 1–7 acts via the Mas Oncogene receptor. This counterbalances the effect of ANG II at AT1R and subsequently the “overstimulation” of the RAS and its pathological consequences [50]. ACE2 is expressed in many organs, especially kidney and lung, and in the cardiovascular system in cardiomyocytes, cardiac fibroblasts, vascular smooth muscle and endothelial cells. It can counteract the effects of RAS, such as inflammation, vasoconstriction, hypertrophy and fibrosis,

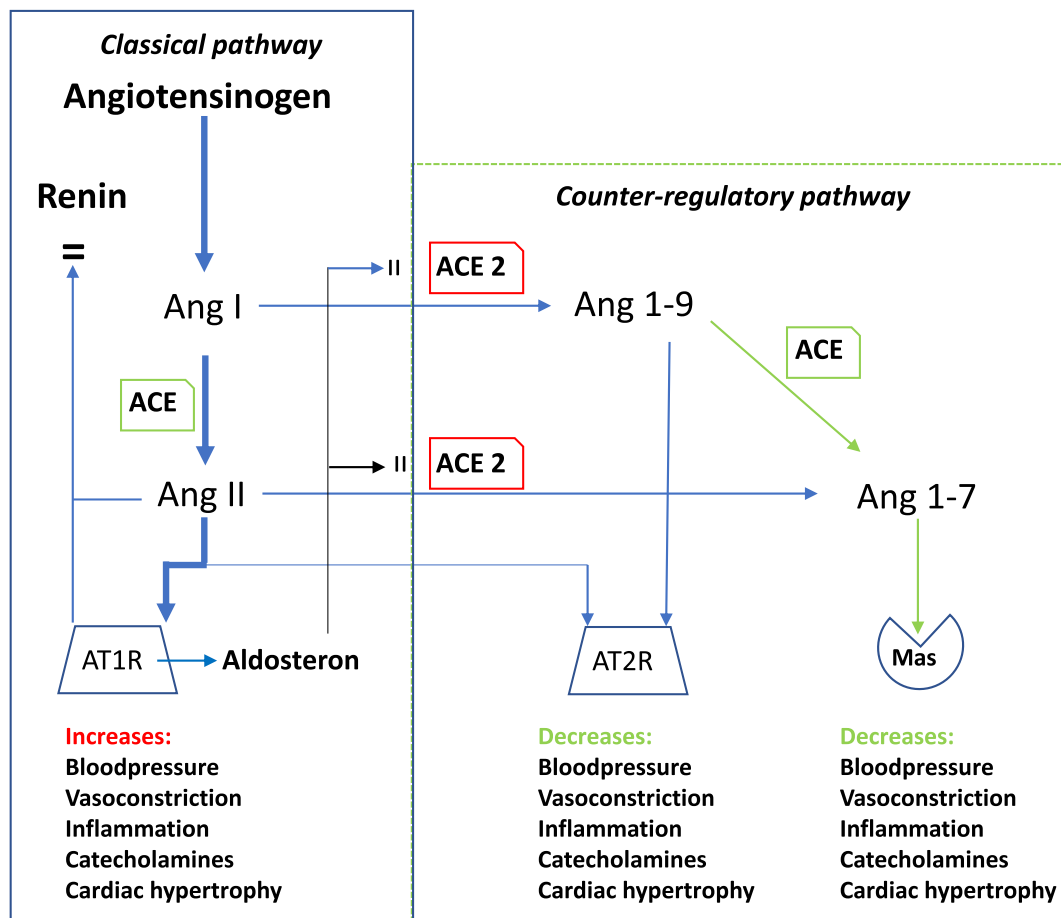


Fig. 1. In the classical RAS pathway Renin, expressed from the renin gene induces cleavage of Angiotensinogen to Angiotensin I which is converted to Angiotensin II via Angiotensin converting enzyme (ACE). Ang II activates the Angiotensin 1 receptor which results in an increase of blood pressure and further effects on the vascular system. In addition, Ang II suppresses renin synthesis via AT1R. To keep the system in balance a counter regulatory pathway exists. This pathway is activated through cleavage of Ang I to Ang 1–9 via ACE2 or AT2R activation or Ang II to Ang 1–7 which counter regulates via Mas receptor. This helps the system to stay within a homeostatic balance, as long as the RAS activity is controlled.

by degrading Ang I and Ang II, thus making them less available for the ACE/AngII/AT1 axis. At the same time ACE2 can strengthen the ACE2/Ang 1–7/Mas axis which attenuates the proinflammatory RAS activation.

1.7. RAS and SARS-CoV-2

Infection with SARS-CoV-2 causes the virus spike protein to come into contact with ACE2 on the cell surface and thus to be transported into the cell. This endocytosis causes upregulation of a metalloproteinase (ADAM17), which releases ACE2 from the membrane, resulting in a loss of the counter regulatory activity to RAS [51]. As a result, proinflammatory cytokines are released extensively into the circulation. This leads to a series of vascular changes, especially in the case of preexisting lesions, which can promote further progression of cardiovascular pathologies.

SARS-CoV-2 not only reduces the ACE2 expression, but also leads to further limitation of the ACE2/Ang 1–7/Mas axis via ADAM17 activation, which in turn promotes the absorption of the virus. This results in an increase in Ang II, which further upregulates ADAM 17. Thus a vicious circle is established turning into a constantly self-generating and progressive process. This process may contribute not only to lung damage (Acute respiratory distress syndrome - ARDS), but also to heart injury and vessels damage, observed in COVID-19 patients. Thus, previous lesions of the cardiovascular system represent a risk factor, since coexisting pathologies can progress as a result of the virus infection

[52,53].

1.8. RAS and vitamin D deficiency

Several studies have shown increased plasma renin activity, higher Ang II concentrations and higher RAS activity as a consequence of low vitamin D status [54,55]. The same applies to the decreasing Renin activity with increasing vitamin D levels [56]. There is an inverse relationship between circulating 25(OH)D and renin, which is explained by the fact that vitamin D is a negative regulator of renin expression and reduces renin expression by suppressing transcriptional activity in the renin gene promoter, thus acting as a negative RAS regulator to prevent overreaction. In VDR knock out mice [57,58]. The 1,25(OH)2D induced repression of the renin gene expression is independent from Ang II feedback regulation.

Permanent increase of the renin levels with an increased Ang II formation has been described, suggesting that in vitamin D deficiency the expression and secretion of renin is increased at an early stage [59,60]. This results in increased fluid and salt intake and rise in blood pressure, that has been explained by an increase in renin and consecutive upregulation of the RAS in the brain [61].

Fig. 2 gives a short description of the impact of vitamin D on RAS.

In a small (open-label, blinded endpoint) study with 101 participants who received 2000 IU vitamin D3 or placebo over 6 weeks, a significant decrease in plasma renin activity and concentration was described [62].

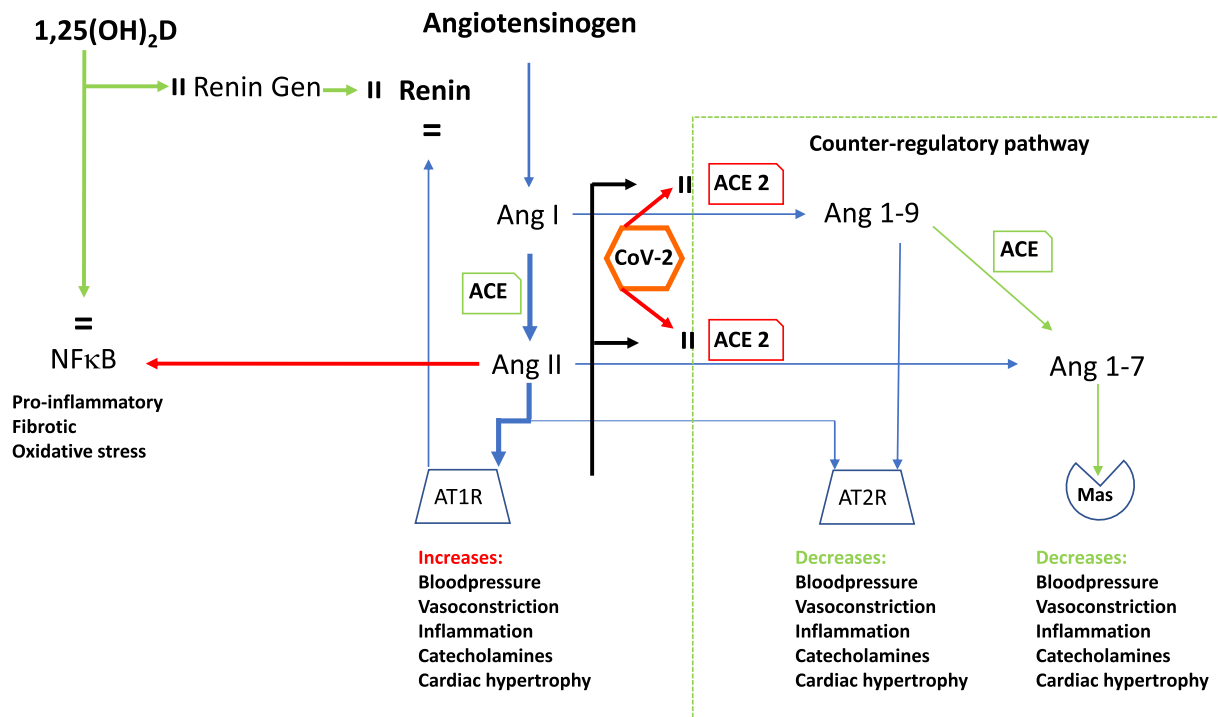


Fig. 2. If the system is dysbalanced this may result in a rising formation of Ang II and a higher renin synthesis which at least increases inflammatory responses. This is important in cases of a poor vitamin D status because vitamin D (1,25(OH)₂D) can counteract the disbalance via negative expression of the renin gen which results in lower renin synthesis independent from Ang II. An increase of aldosterone will block the activities of the ACE2 and as a consequence attenuate the counter regulatory balance. If the counter regulatory circle is disrupted via ACE2 dysfunction due to SARS-CoV2 infection an uncontrolled classical pathway will run out of control and increase proinflammatory reactions and blood pressure and contribute to a couple of problems (e.g. cardiovascular, ARDS, Kawasaki disease). Ang II activates NFκB through AT1 receptors [194]. This and further interactions of the RAS with inflammatory stimuli results in an increasing and less controlled inflammatory reaction. Beside its effect on renin expression vitamin D can effectively inhibit NFκB activation [195]. This is especially efficient when the VDR is upregulated, which also plays an important role in other processes in the immune system through vitamin D activity.

The EVITA study examined the effect of vitamin D supplementation (4000 IU/day) over 36 months [63]. No relationship was found between blood levels of 1,25(OH)₂D and various parameters of the RAS (renin, aldosterone) and vitamin D plasma levels increase. Rather, vitamin D supplementation led to an increase in renin in a subgroup that initially had a mild deficiency of vitamin D. The 25(OH)D value in these subgroups increased from 20.4 nmol/L to 83.7 nmol/L after 36 months. Renin from 859 mIU/L to 1656 mIU/L. It cannot be excluded that these were rather toxic effects of a dose in the upper level range. However, the fact that blood levels increase naturally reduced the renin concentration become clear when looking at the placebo group with initial hypovitaminosis D (21.3 nmol/L) with a strong increase after 36 months (45.6 nmol/L). Renin decreases from the initial value of 507 to 430 mIU/L after 36 months. According to this, a moderate suppressive effect of vitamin D is conceivable under physiological conditions and in particular in participants with a compensated vitamin D deficiency. The plasma level of renin and 1,25(OH)₂D show a significant inverse correlation in hypertensive individuals [64]. In a study on 184 normotensive participants, higher circulating Ang II levels were associated with decreasing 25(OH)D blood levels. After infusion of Ang II there was a blunted renal blood flow, both effects were considered RAS activation in the setting of lower plasma 25(OH)D [65].

1.9. Vitamin D, blood pressure, and COVID-19 mortality

Vitamin D supplementation leads to a reduction in blood pressure in patients with essential hypertension [66,67], and to a reduction in blood pressure, plasma renin activity and angiotensin II levels in patients with hyperparathyroidism [68,69]. Low vitamin D status may contribute to increased activity of the RAS and subsequent higher blood pressure. An inverse relationship between the concentration of the

active metabolite 1,25(OH)₂D₃ and blood pressure has been described in hypertensive as well as normotensive individuals [70,71]. In a study using the mendelian randomization approach in 35 trials (146,581 participants) with four SNPs (Single Nucleotide Polymorphism), a causal relationship was shown between increasing 25(OH)D levels and decreased risk of hypertension in individuals with genetic variants leading to low Vitamin D plasma levels [72].

Depending on the study, the number of COVID-19 patients affected with hypertension was between 20 and 30% and the proportion of diabetics between 15 and 22% [73]. Data from 5 studies in Wuhan (n:1458) reported 55.3% and 30.6% cases respectively of hypertension and of diabetes [74]. 49% of the 1591 patients in ICUs in Italy (Lombardy), 1287 of whom needed respirators, had hypertension and were older than the normotensive ones [75].

Hypertension, followed by diabetes (16.2%), was the most frequent concomitant morbidity in patients with severe course disease [76,77,78].

1.10. Vitamin D and cardiovascular diseases

Vitamin D has multiple functions in the cardiovascular system and thus represents an important protective factor of endothelial, vascular muscle, and cardiac muscle cells [79]. In a meta-analysis of 65,994 participants an inverse relationship between 25(OH)D vitamin D plasma levels (below 60 nmol/L) and cardiovascular events was shown [80]. These findings have been confirmed by the Framingham and NHANES data [81,82]. As for the positive effects on respiratory diseases shown by vitamin D supplementation, also for cardiovascular disease positive effect was reported only if there was a vitamin D-deficit before supplementation.

In a large cohort of patients (n = 3296) referred to coronary

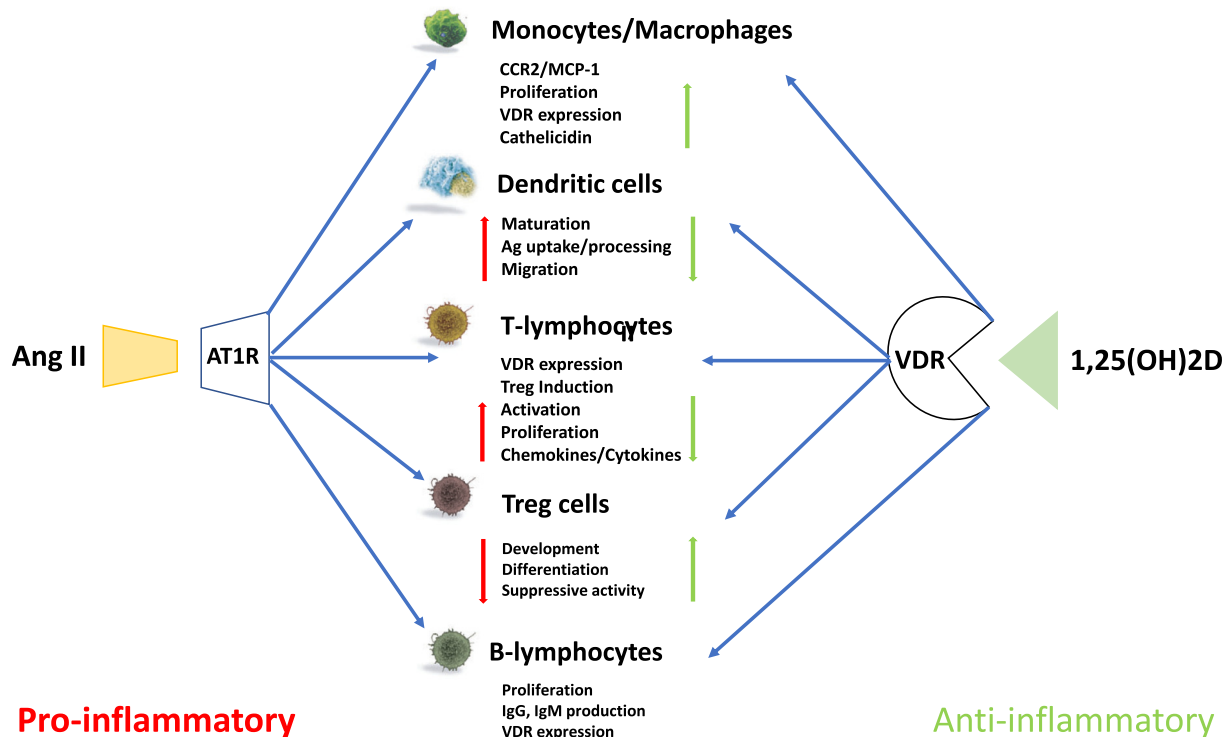


Fig. 3. Ang II leads to a series of pro-inflammatory stimuli in the immune system via the activation of AT1R. These include an increase in the expression of MCP-1 as well as the chemokine receptor CCR2, which lead to a massive infiltration of the endothelium with macrophages. The same applies to the activation, migration and maturation of dendritic cells (DC) and the antigen (Ag) presentation. The negative effect on T lymphocytes as well as on T regulatory cells further promotes a pro-inflammatory state. A number of other proinflammatory processes are triggered by AT1R and favor the development of inflammation, hypertension and diabetes. Vitamin D is considered to counteract this reaction by contributing to a normalization of immune function through a variety of processes. However, it should not be overlooked that most processes in the immune system initiated by vitamin D occur together with vitamin A [196].

angiography, a significant increase in plasma renin and angiotensin II was observed with decreased 25(OH)D and 1,25(OH)2D levels, but not with circulating aldosterone levels [83]. Vitamin D plasma levels are an independent risk factor for CVD mortality. 92% of 1801 patients with metabolic syndrome, had a low vitamin D status (22.2% were severely deficient (25(OH)D < 25 nmol). CVD mortality and total mortality were reduced respectively by 69% and 75% in those with highest 25(OH)D levels (> 75 nmol/L) [84].

CVD is considered an independent risk factor for fatal outcome in COVID-19 patients. The proportion of survivors with CVD was 10.8%, among non-survivors 20% [85]. Disturbed coagulation, endothelial dysfunction and proinflammatory stimuli described as a result of a viral infection are considered to be among the major causes [86].

1.11. Vitamin D, obesity and type II diabetes

Obesity (BMI > 30 kg/m²) is often associated with low 25(OH)D plasma level [87,88]. Using a bi-directional genetic approach, 26 studies (42,024 participants - Caucasians from Northern Europe and America), including 12 SNPs, showed that higher BMI (Body Mass Index) leads to lower 25(OH)D plasma levels. The repeatedly discussed hypothesis that low 25(OH)D level leads to increased BMI could not be verified [89]. Obesity is therefore another risk factor for an insufficient vitamin D status independent from age [90].

Low 25(OH)D plasma values are also found in diabetes II [91,92]. This is often associated with an increased risk of metabolic syndrome, hypertension and cardiovascular diseases [93,94]. One of the main causes could be insulin resistance, often found in connection with low vitamin D levels [95]. This is well documented by the evaluation of observational and intervention studies using metabolic indicators. 10 out of 14 intervention studies showed a positive effect of Vitamin D on

metabolic indicators [96]. Vitamin D deficiency is therefore also considered to be a potential link between obesity and diabetes type II [97].

Via a short-loop feedback Ang II inhibits the further release of renin via AT1R.

If the renin secretion is not sufficiently inhibited, an overreaction of the RAS can lead to a further increase in blood pressure, increased sodium reabsorption, increased aldosterone secretion and thus increased insulin resistance [98]. This overreaction is considered to be a major cause of the development of hypertension, diabetes and cardiovascular disease, especially in people with high BMI, since adipose tissue contributes to an overreaction of the RAS [99]. Adiponectin synthesis in adipocytes counteracts most of these effects, however circulating levels are inversely related to BMI [100,101]. Vitamin D can regulate the formation and release of adiponectin [102,103]. Obese people often have low adiponectin and vitamin D levels and an inverse relationship between fat mass and vitamin D levels has been described [104]. Therefore, vitamin D deficiency might explain RAS overreaction and following consequences [105].

In a small study on 124 IUC patients with SARS-CoV-2 it was found that obesity (BMI > 35 kg/m²) occurred in 47.6% of the cases and severe obesity (BMI > 35 kg/m²) in 28.2% [106]. In the latter case, 85.7% had to be mechanically ventilated invasively, 60 patients (50%) had hypertension, 48 of these (80%) had to be ventilated invasively. A study from Shenzhen, China also confirmed that obesity is a risk factor for severe course of disease. In a cohort of 383 patients with COVID-19, overweight patients (BMI 24–27.9) had 86% higher risk of developing pneumonia and obese patients (BMI > 28) had 142% higher risk of developing pneumonia compared to normal weight patients [107].

1.12. Vitamin D and ARDS (adult respiratory distress syndrome)

The main cause of death in COVID-19 patients is ARDS. Patients (without COVID-19) (mean age 62 Y) with ARDS (n:52) and those at high risk of ARDS (n:57) (esophagectomy) had low (27.6 nmol/L) to very low (13.7 nmol/L) 25(OH)D blood levels as a sign for severe vitamin D deficiency [108].

ACE2 exerts a counter-regulation of the harmful effect of ACE. Ultimately, it would then be the balance between ACE and ACE2 that explains the reaction of the RAS. The ACE2 effect on the RAS is shown in experimental studies in which ACE2 knock out mice developed severe lung disease with increased vascular permeability and pulmonary edema [109]. Over-expression or the use of recombinant ACE2 improves blood flow and oxygenation and inhibits the development of ARDS after LPS-induced lung damage [110,111].

The development of ARDS shows typical changes in membrane permeability of the alveolar capillary, progressive edema, severe arterial hypoxemia and pulmonary hypertension [112]. The same changes can be achieved in animal experiments by injection of lipopolysaccharides (LPS) [113]. Vitamin D significantly attenuates the lung damage caused by LPS. LPS exposure leads to a significant increase in the pulmonary expression of renin and ANGII. This promotes the pro-inflammatory effects of the conversion of AngII via AT1R and suppresses ACE2 expression. The administration of vitamin D was able to reduce the increased renin and AngII expression and thus significantly lower the lung damage. The authors conclude that this may have been due to the reduction of the renin and ACE/AngII/AT1R cascade and the promotion of ACE2/Ang1–7 activity by vitamin D through its influence on renin synthesis.

Increased ACE and ANGII expression and reduced ACE2/Ang1–7 expression in lung tissue favors lung damage induced by ischemia reperfusion in mice [114]. The ACE/Ang1–7 expression and the amount of circulating Ang 1–7 was increased at the onset of ischemia and then decreased rapidly in contrast to the tissue concentration, while AngII increased. This suggests a dysregulation of local and systemic RAS. The application of recombinant ACE2 was able to correct the dysregulation and attenuate the lung damage, while ACE2 knock out increased the imbalance and was associated with more severe damage. Inhibition of the ACE/AngII/AT1R pathway or activation of the ACE2/Ang1–7 pathway have therefore been proposed as therapeutic options.

In rats with LPS-induced acute lung injury (ALI), the administration of vitamin D (calcitriol) was associated with a significant reduction in clinical symptoms of ALI. Calcitriol treatment led to a significant increase in the expression of VDR mRNA and ACE2 mRNA. VDR expression may have resulted in a reduction of angiotensin II, ACE2 expression in increased anti-inflammatory effects [115].

VDR is not only a negative regulator of renin, but also of NFκB [116], leading both to an increase in Ang II formation [117], which in turn promotes pro-inflammatory cascades. Furthermore SARS-CoV-2 infects T-lymphocytes [118] and the Covid-19 disease severity seems to be related to lymphopenia [119], which occurs in 83,2% of COVID-19 patients at hospital admission [120]. Indeed, in a recent meta-analysis on 53.000 COVID-19 patients decreased lymphocyte count and increased CRP were highly associated with severity [121].

Regulatory T cells (Treg) play an important role in the development of ARDS [122]. They can attenuate the pro-inflammatory effects of the activated immune system. Vitamin D increases the expression of Treg cells and supplementation of healthy volunteers results in a significant increase in Tregs [123]. Vitamin D causes a reduction in pro-inflammatory cytokines by inhibiting B- and T-cell proliferation [124,125]. Inflammatory processes also play an important role in the development of hypertension and CVD [126,127]. Here, an interesting but so far not proven connection between vitamin D and RAS is found. T-cells have a RAS system, which contributes to the generation of reactive oxygen species (ROS) and the development of high blood pressure through the formation of Ang II [128]. To what extent vitamin D in

T cells is also a negative regulator of renin is not known, but could be one of the reasons for the anti-inflammatory effect [129].

1.13. Cytokine storm: Vitamin D, SARS-CoV-2, and ACE2

In patients with a severe disease course (ARDS) a cytokine storm is assumed to be the underlying cause [130]. SARS CoV-2 can lead to a downregulation of ACE2 in the lungs and to a shedding of the ectodomain of ACE2. This soluble sACE2 shows enzymatic activity, but the biological role is unclear. The soluble form is believed to exert systemic influence on angiotensin II [131]; since SARS-CoV-2 induces shedding, it is assumed that sACE2 is directly related to the virus-induced inflammatory response [132].

Downregulation of ACE2 expression by SARS-CoV infection is associated with acute lung damage (edema, increased vascular permeability, reduced lung function) [133] and with RAS dysregulation leading to increased inflammation and vascular permeability. Inflammatory cytokines such as TACE (TNF- α -converting enzyme) induce increase shedding [134], which in turn can be also caused by spike protein of the virus, promoting virus uptake by ACE2 [135]. Comparative studies on mortality rates in different countries and analysis of the relationship between vitamin D and CRP (as a marker of cytokine storm) plasma levels, concluded that.

risk factors for severity of the clinical course, predicted by high CRP and low vitamin D (< 25 nmol) levels, were reduced by 15.6% following vitamin D status normalization (> 75 nmol) [136]. It is interesting to note that calmodulin kinase IV (CaMK IV) stimulates vitamin D receptor (VDR) transcription and interaction with co-activator SRC (steroid receptor coactivator) [137]. According to the authors, this would explain the linkage of the genomic and non-genomic membrane pathways of vitamin D. The calmodulin binding domain at ACE2 [138] may explain why calmodulin inhibits the shedding of the ectodomain of ACE2 [139]. It is also conceivable that vitamin D may show significant effects either by stimulating VDR-mediated transcription, or by mediating 1,25(OH)D calcium-dependent activity through CaMK II and phospholipase A [140].

1.14. Kawasaki syndrome

Children and adolescents rarely show severe disease courses. A meta-analysis comprising 18 studies with 444 children under 10 years of age and 553 between 10 and 19 years of age, reported only one case of severe complication in a 13-year-old child. In North America, 48 cases of children (4.2–16.6 yrs) have been described with severe disease course. Independently of this, COVID-19 children have a clinical picture that has not been associated with usual acute clinical manifestations of SARS-CoV-2 infection, showing an unusually high proportion of children with gastrointestinal involvement, Kawasaki disease (KD) like syndrome, until now [141].

KD is an acute vasculitis which can lead to aneurysms of the coronary arteries and is considered the leading cause of acquired heart disease in children [142]. A number of cases have been observed in recent weeks suggesting a relationship between Kawasaki syndrome and COVID-19 [143].

One reason probably relies upon ACE gene polymorphisms [144]. In these polymorphisms there is a strong increase in ACE without affecting AngII plasma levels [145]. There is a direct relationship between ACE polymorphism (with high ACE plasma levels) and the occurrence of KD, according to a recent meta-analysis [146].

Irrespective of this, the disease occurs seasonally during the winter months in extratropical northern atmosphere and is often associated to respiratory tract infections [147]. A KD associated Antigen was found in proximal bronchial epithelium in 10 out of 13 patients with acute KD and in a subset of macrophages of inflamed tissues [148]. That strengthens the hypothesis that an infectious agent entering the respiratory tract, might be the cause of KD. Indeed, it was reported that

children with KD were affected by respiratory diseases with HCoV: New Haven coronavirus [149]. The authors concluded that there was a significant association between KD and HCoV-NH infection.

Just like current evidence suggest that vitamin D-deficiency is associated with increased risk of CVD, including hypertension, heart failure, and ischemic heart disease, patients with KD also show very low vitamin D levels. Children with KD (79) had significantly lower 25(OH)D levels (9.17 vs 23.3 ng/ml) compared to healthy children of the same age [150].

Intravenous immunoglobulin (IVIG) has become the standard therapy for KD [151], with a good therapeutic response from young patients, of which only 10–20% need additional anti-inflammatory medication [152]. In a study on 91 KD children, 39 of them with very low plasma vitamin D levels (< 20 ng/ml), showed immunoglobulin resistance compared to the rest of the children ($n = 52$) children with higher levels (> 20 ng/ml) [153]. Children with immunoglobulin resistance also have a higher incidence of coronary artery complications [154,155].

The relationship between ACE polymorphism and peripheral vascular disease is observed in Asians but not in Caucasians [156,157]. Furthermore the prevalence of KD in Japan (240/100,000) is 10 times higher than in North America (20/100,000) [158,159]. During February and April 2020, 10 cases of COVID-19 and KD were reported in Bergamo, Italy, corresponding to 30 times higher rate than the last 5 years incidence [160]. The higher incidence of KD in Asian children (35.3 cases/100,000) as reported in California, may indeed indicate a more frequent ACE polymorphism in Asian population, followed by African-Americans (24.6/100,000) probably due to the fact that pigmentation reduces vitamin D production in the skin [161] compared to white children (14.7/100,000). From 189 children hospitalized between 1991 and 1998 136 (72%) of the children were African-American and 43 (23%) were white [162]. It is conceivable that Vitamin D deficiency which activates the RAS, promotes the development and course of KD.

1.15. Therapeutic aspects

1.15.1. Vitamin D status

The aim of a therapy with vitamin D should be a normalization of the vitamin D status, preferably > 75 nmol/L. Basically, it can be assumed that a vitamin in physiological doses can do little more than remedy the symptoms or secondary manifestations of a deficiency. Vitamin D is a prohormone. Therefore, the question of correcting the status should be treated in the same way as for other hormones (e.g. thyroid hormone). Before starting therapy, the plasma level should be determined. This allows a dosage and therapy to be initiated that corresponds to the respective status. The analysis should be carried out especially in risk groups (Table 1) in order to be able to react adequately, especially in acute cases. The general recommendation to supplement with a recommended daily dose (800 IU) may apply to people who do not belong to a risk group, are healthy.

The vitamin D status is the basis for treatment with vitamin D. There are indeed, risk groups were a poor status can be expected.

As it is known that the amount of 25(OH)D circulating in the blood

Table 2
Threshold levels to calculate deficiency ranges (25(OH)D).

| Severe | < 12.5 nmol/L | < 5 ng/ml |
|------------|----------------|---------------------------|
| Moderate | 12.5–29 nmol/L | 5–11.6 ng/ml |
| Mild | 30–49 nmol/L | 12–19.6 ng/ml |
| Sufficient | > 50 nmol/L | > 20 ng/ml ¹⁶⁵ |
| | > 75 nmol/L | > 30 ng/ml ¹⁶⁶ |
| Toxicity | > 250 nmol/L | > 100 ng/ml |

and less the active metabolite 1,25(OH)2D is a better indicator for a deficit, threshold values have been set here (Table 2).

A vitamin D status below 20 ng/ml or < 50 nmol/L should be treated to achieve a minimum level of 30 ng/ml (75 nmol/L). Values around 75 nmol/L are considered optimal, with respect to the skeletal activities [167]. Particularly in countries where vitamin D fortified foods are not available, the importance of an adequate supply should be emphasized. A sufficient vitamin D status can be achieved in the healthy populations following the recommendations and the thresholds of the plasma levels. In case of comorbidities related to the clinical development of COVID-19 there might be a higher need and therefore it is discussed to choose other recommendations for the adequate care of persons with chronic diseases [168,169].

A recent meta analysis related to vitamin D and respiratory tract infections showed that a daily or weekly Vitamin D dose between 20µg and 50µg resulted in a significant reduction of infections [170]. An isolated or added bolus with high doses (2.5 mg once or monthly) did not reduce risk. One study supplemented adults with high risk for ARDS with a 100µg/daily for one year [171]. The overall infection score was significantly reduced in the treated group. Those with an initial vitamin D deficit showed the greatest benefit of the supplementation. With respect to COVID-19 a recommendation for primary prevention of vitamin D deficiency seems meaningful. Whether this will be prevention against COVID related diseases remains speculative. If a patient belonging to a risk group is delivered to the hospital, vitamin D status should be immediately assessed and in case of insufficiency (< 50 nmol/L) or deficiency (< 25 nmol/L) higher doses might be needed as recommended by the NHS [172].

The recommendations of the National Health Service UK are based on those of various professional associations. It should be noted that vitamin D therapy is contraindicated for patients with hypercalcemia or metastatic calcification. Suggested therapy should be used when low plasma levels and the following symptoms are present:

- muscle pain
- Proximal muscle weakness
- Rib, hip, pelvis, thigh and foot pain (typical)
- Fractures.

So far, there is no experience on the use of vitamin D in COVID-19. The observation that a normal vitamin D status is important for the immune system as well as for the regulation of the RAS should, however, lead to a correction of the Vitamin D status if a deficiency is detected. Nevertheless, it should be borne in mind that high doses of

Table 1
Risk factors for deficiency (NHS) [163].

| Inadequate skin synthesis | Poor oral supply | Co-Morbidities |
|--|----------------------|---------------------------|
| Air pollution | Vegetarian or fish | Reduced synthesis |
| Northern latitude/Winter | Free diet | Increased breakdown |
| Occlusive garments | Malabsorption | Drugs: rifampicin, HAART- |
| Pigmented skin | Short bowel | Therapy, ketoconazole |
| Habitual sunscreen use | Cholestatic jaundice | Anticonvulsants |
| Institutionalized/housebound and people with poor mobility | Pancreatitis | Glucocorticoids |
| Age > 65 | Celiac disease | CKD (eGFR < 60) [164] |

vitamin D also carry risks, as they can contribute to changes in VDR competence and thus have an inhibitory effect on immune function (Ref: Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. *Inflkamm Res* 2014; 63: 803-811)

The importance of a vitamin D deficiency is shown by a recently published analysis of the COVID-19 deaths of 780 COVID-19 patients in Indonesia [173].

table 3 data of patients with COVID-19 related to vitamin D levels and disease outcome

| | Vitamin D: < 20 ng/ml | 20-30 ng/ml | > 30 ng/ml |
|---------------------------------------|--------------------------|-------------|-------------|
| Overall, N | 179 | 213 | 388 |
| Mean age | 66.9 ± 13.8 | 62.9 ± 14.7 | 46.6 ± 12.6 |
| Comorbidity, % | 80.0 | 73.8 | 18.8 |
| Death, % | 98.9 | 87.8 | 4.1 |
| Active, % | 1.1 | 12.2 | 95.9 |
| Odds ratio | 10.12 (p < .001) | 7.63 | |
| Adjusted for age, sex and comorbidity | | (p < .001) | |

The table illustrates that old age, comorbidities and vitamin D deficiency or insufficiency contributed to outcome of the disease. Based on these data Vitamin D plasma level is an independent predictor of mortality.

1.15.2. VDR agonists (VDRA)

VDRA are discussed to counteract the effect of imbalanced immune response and have suppressant effects on the RAS. Since VDRA have been observed to contribute to a significant reduction of inflammatory processes, they are increasingly used in immunosuppressive therapy to control TH1-related overreactions via interaction of VDRA with the chemokine CXCL10, a T cell chemoattractant chemokine [174]. The induction of CXCL10 is an important step against bacterial and virus infections. However, sustained CXCL10 induction leads to amplified neuroinflammation in Coronavirus (JHMV) induced neurologic infection [175]. CXCL10 is also considered a critical factor in ARDS. H5N1 influenza infection in mice resulted in increased CXCL10 secretion with a consequent inflamed neutrophils massive chemotaxis and a subsequent pulmonary inflammation [176]. Following SARS-CoV-2 infection, CXCL10 and other chemo- and cytokines are upregulated [177]. Anti CXCL10 antibodies have shown ARDS improvement following LPS induced lung injury with high CXCL10 levels [178].

Additionally evidence from animal models (diabetic nephropathy) has shown that VDRA block TGFβ system in the glomerulus and thus abolish interstitial fibrosis [179]. It is assumed that VDRA modulates increased RAS activity. Indeed, a clinical study on 281 patients (type II diabetes with albuminuria) revealed that VDR activator paricalcitol (19-nor-1,15-dihydroxyvitamin D₂) led to a significant albuminuria reduction as well as a decrease in blood pressure despite increased salt intake, as a sign of decreased RAS activity [180]; effect that could not be achieved with losartan (ANG II receptor antagonist) [181].

1.15.3. Morphine

Morphine medication is an essential part of treatment for COVID patients with severe ARDS. It is used early for dyspnea or pain and for shivers [182]. Morphine, at doses similar to those used in humans, can lead to downregulation of VDR in human T cells and activation of RAS with renin upregulation and a threefold increase in Ang II production, resulting in increased reactive oxygen species (ROS) responsible for DNA damage and T cells apoptosis.

VDR agonist (EB1089) inhibits VDR downregulation, leading to RAS decreased activity, inhibition of morphine induced ANG II production, reduced ROS formation and lower DNA damage, thus inhibiting T-cell apoptosis [183]. In addition, if Jurkat cells were pretreated with EB

1089 and Losartan, an Angiotensin II receptor antagonist (ARB) before incubation with morphine. The combination of the Vitamin D Receptor agonist and Losartan attenuated the morphine-induced ROS formation. Indeed, as an example ARB increase ACE2 expression [184] and Ang 1–7/Mas axis activation reduced ROS formation [185].

1.15.4. Autophagy, spermidine and vitamin D

Spermidine is a metabolite of polyamines which are delivered through the diet and partially metabolized by colon bacteria from undigested proteins. Polyamines can influence macrophages development into pro-inflammatory or anti-inflammatory type by altering cellular metabolism and triggering mito- and autophagy [186]. The capacity of spermidine to ensure proteostasis through the stimulation of the cytoprotective autophagy is acknowledged as one of its main features.

Recently, the effect of spermidine on autophagy in SARS-CoV-2 infected cells which results in inhibition of autophagy has been described [187]. Since spermidine promotes autophagy, spermidine and other agents may be a therapeutic approach to SARS-CoV-2 infection.

With regard to the specific risk of elderly to develop severe course of SARS-CoV-2 infection, it is interesting to note that spermidine concentrations in organs and cells decline with age and resulting in a decrease of autophagy [188]. Consumption of LKM512 yogurt increases spermidine synthesis in the gut in elderly [189]. Whether that has any impact on supply of spermidine to enterocytes or other tissues remains to be elucidated. Spermin and spermidine but not putrescine another polyamine metabolite can activate VDR in vitro within their physiological intracellular concentrations [190]. Vitamin D and VDR play an important role in autophagy. Vitamin D can induce autophagy similar to spermidine by inhibiting mTORC1 complex activation [191] and by increasing Beclin-1 expression, similar to spermidine [192].

2. Limitations

A major limitation of all studies dealing with low levels of vitamin D and disease is the fact that there are only few studies, which show a causal relationship. Most studies show associations and data regarding the influence of COVID-19 on vitamin D status are missing. Furthermore, it should not be overlooked that many of the effects of vitamin D on gene expression in the immune system occur together with vitamin A. The effect of vitamin A deficiency in COVID-19 has not yet been investigated. However, vitamin A deficiency or combined deficiencies with vitamin D or other micronutrients exists not only in low income countries.

3. Conclusion

An inadequate supply of vitamin D has a variety of skeletal and non-skeletal effects. There is ample evidence that various non-communicable diseases (hypertension, diabetes, CVD, metabolic syndrome) are associated with low vitamin D plasma levels. These comorbidities, together with the often concomitant vitamin D deficiency, increase the risk of severe COVID-19 events. Much more attention should be paid to the importance of vitamin D status for the development and course of the disease. Particularly in the methods used to control the pandemic (lockdown), the skin's natural vitamin D synthesis is reduced when people have few opportunities to be exposed to the sun. The short half-lives of the vitamin therefore make an increasing vitamin D deficiency more likely. Specific dietary advice, moderate supplementation or fortified foods can help prevent this deficiency. In the event of hospitalisation, the status should be urgently reviewed and, if possible, improved.

In the meantime, 8 studies have started to test the effect of supplementing vitamin D in different dosages (up to 200,000 IU) on the course of the COVID-19 disease. The aim is to clarify whether supplementation with vitamin D in different dosages has an influence on the course of the disease or, in particular, on the immune response, or

whether it can prevent the development of ARDS or thromboses [193].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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