Vitamin D and acute and severe illness – a mechanistic and pharmacokinetic perspective

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Abstract

The COVID-19 pandemic has generated high interest in factors modulating risk of infection, disease severity and recovery. Vitamin D has received interest since it is known to modulate immune function and vitamin D deficiency is associated with increased risk of respiratory infections and adverse health outcomes in severely ill patients. There are no population representative data on the direct relationship between vitamin D status and SARS-CoV-2 infection risk and severity of COVID-19. Data from intervention studies are limited to 4 studies. Here we summarise findings regarding vitamin D status and metabolism and their alterations during severe illness, relevant to COVID-19 patients. Further, we summarise vitamin D intervention studies with respiratory disease outcomes and in critically ill patients and provide an overview of relevant patient and population guidelines. Vitamin D deficiency is highly prevalent in hospitalised patients, particularly when critically ill including those with COVID-19. Acute and critical illness leads to pronounced changes in vitamin D metabolism and status, suggestive of increased requirements. This needs to be considered in the interpretation of potential links between vitamin D status and disease risk and severity and for patient management. There is some evidence that vitamin D supplementation decreases the risk of respiratory tract infections, while supplementation of ICU patients has shown little effect on disease severity or length of treatment. Considering the high prevalence of deficiency and low risks associated with supplementation, pro-actively applying current population and patient management guidelines to prevent, monitor and correct vitamin D deficiency is appropriate.

Introduction

The coronavirus disease 2019 (COVID-19) is causing worldwide morbidity and mortality. The aetiology and progress of the –initially- respiratory disease in those severely affected is complex and affects many organ systems. Disease severity varies widely between affected individuals, from an asymptomatic course or mild symptoms to an overwhelming multisystem illness with high mortality. Those who are older, obese and those with major pre-existing health conditions (including cardiovascular disease and diabetes) are at greatest risk(1-5). In addition to a high incidence of acute respiratory distress syndrome (ARDS), the virus poses particular risks of both arterial and venous thromboembolism and of haemorrhagic complications: pulmonary embolism and stroke are important causes of death. Endothelial damage may also contribute to the high incidence of acute kidney injury (AKI). Immune dysfunction underlies the catastrophic "cytokine storm" which can be a terminal event (1, 4, 6). Several therapeutic interventions, particularly those that control cytokine production, have recently been shown to reduce mortality in patients with a severe disease course (4, 7-9). Vaccination programmes are currently rolled out globally. Until the time that a large proportion of the world population has acquired immunity, infection prevention and reduction of disease severity is paramount, in view of the severe disease process with long rehabilitation time in many patients (10).

Vitamin D has received increased interest since it is known to modulate immune function and the inflammatory response and vitamin D deficiency is associated with increased risk of respiratory infections (10-15) and adverse health outcomes in severely ill patients (16, 17). It may therefore be involved in both susceptibility and progression of respiratory disease. No good quality, population representative data on the relationship between vitamin D status and SARS-CoV-2 infection risk and severity of COVID-19 disease, exist. The first findings from 3 intervention studies in hospitalised COVID-19 patients supplemented with vitamin D were recently published (18-20) and several randomised controlled trials (RCTs) in diverse population or patient groups are ongoing (10, 21, 22).

Vitamin D status is measured as the plasma concentration of 25 hydroxy vitamin D (25(OH)D). Deficiency thresholds for population health are defined as 25(OH)D serum concentrations <25 or 30 nmol/L per UK and US guidelines. Thresholds or target values for 25(OH)D may be set higher for clinical management and specific patient groups (23-25). Vitamin D status has been shown to be associated with many health outcomes but for many chronic diseases other than musculoskeletal health, intervention trials are less consistent and often do not confirm findings of observational studies (26-28). This can potentially partly be ascribed to the confounding effects of vitamin D supply from other

sources than the intervention given in RCTs (i.e. vitamin D supply through cutaneous sun exposure and from food and supplements), vitamin D uptake in and potential mobilisation from bodily stores and the complex nature of vitamin D metabolism. Vitamin D status is therefore influenced by factors associated with lifestyle and fitness. In addition, status is affected by pathological changes occurring during acute and chronic illness. Therefore, causality and reverse causality are difficult to distinguish. Further, the effect of interventions may depend on baseline and post-supplementation vitamin D status, but also results considering 25(OH)D before and after supplementation are conflicting (29-32).

The role of vitamin D and the effect of supplementation has also been investigated in studies and intervention trials with respiratory disease outcomes and critically ill patients. These are likely relevant for the current COVID-19 epidemic.

Here we summarise recent findings regarding vitamin D status and metabolism in patients, with a particular focus on those severely ill and with COVID-19. The effect of vitamin D supplementation on respiratory disease and critically ill patients are described in the context of alterations of vitamin D metabolism and requirements with severe illness. We also provide an overview of guidelines to correct and maintain vitamin D status for specific categories of patients and the prevention of vitamin D deficiency in population groups.

COVID-19, vitamin D status and supplementation

The recent COVID-19 epidemic identified a high prevalence of vitamin D deficiency amongst patients (33), particularly those that develop severe symptoms of the disease (34-39). Vitamin D deficiency (25(OH)D< 30nmol/L) at hospital admission (n=185) was associated with increased hazard ratio to require invasive mechanical ventilation and death in one study (40), but this was not found in another, slightly smaller study (n=109)(41). Patients at increased risk of requiring ICU admission and ventilation appear to be carriers of common risk factors for vitamin D deficiency, i.e. being overweight or obese, having Type 2 diabetes, hypertension and chronic kidney disease (2, 3, 36, 42), but vitamin D status has also been reported to be an independent predictor after adjustment for confounding factors (37, 40). This raises the question whether vitamin D deficiency is a risk factor for this viral infection and/or developing severe disease symptoms, is a biomarker of poorer health or that the disease process is associated with a decrease in vitamin D status as outlined below. In several countries (the US and UK) overrepresentation of ethnic minorities testing positive and/or developing severe symptoms is

reported (3, 39, 43-46) (https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/ethnicity-and-outcomes-of-covid-19-patients-in-england). The higher prevalence of severe illness in specific ethnic minority groups in the US and UK, countries with temperate climates, has been suggested to be related to their generally lower vitamin D status, due to lower rate of cutaneous vitamin D production associated with a darker skin tone. Many other factors may also play a role, including higher risk of obesity, hypertension, T2DMM, elevated inflammation markers and renal impairment in these groups (47). Individuals of specific racial descent may potentially also have different responses to infection and treatment and may require different treatment strategies. In addition, overrepresentation of these groups in professions with high exposure risk, differences in access and use to health care systems and other socio-economic factors may play a key role in some areas (45, 48). Country differences in the prevalence of COVID-19 between ethnic groups may also reflect differences in population diversity and characteristics and health care systems.

There are no prospective data available that directly allow the investigation of the protective role of vitamin D status, intake and supplementation in the prevention of infection with SARS-CoV-2 at the time of viral exposure and subsequent development of COVID-19 symptoms. Two studies with retrospective data from the population-based UK BIOBANK showed that plasma 25(OH)D measured 10-14 years before the COVID-19 outbreak was not associated with the risk of developing moderate to severe symptoms of the disease after the correction for appropriate confounders (44, 49, 50). In univariate models, Hastie (50), but not Raisi- Estabragh found an increased odds ratio of COVID positivity with lower plasma concentrations of 25(OH)D but this did not remain significant after correction for range of confounders (BMI, age, ethnicity and season) and co-morbidities. Other retrospective studies used large data sets from clinical laboratories and medical records. Kaufman et al (46) reported a significant negative association between the percentage of patients testing positive for SARS-CoV-2 and season-corrected plasma 25(OH)D measured within a year prior to SARS-CoV-2 infection. In subgroup analyses, Kaufman presented data by ethnic group (as based on predominance of ethnicity by postcode area), showing (a) a higher COVID positive incidence rate and (b) a lower plasma 25(OH)D concentration in postcodes with predominantly black and Hispanic communities compared to predominantly white communities, but (c) the association with 25(OH)D was negative and significant in all three groups. Meltzer conducted 2 retrospective studies using large data sets from clinical laboratories and medical records. They included individuals who had a COVID-19 PCR test following potential COVID-19 symptoms or exposure and if assessed for vitamin D status within 1 year before the COVID test. In the 2020 study Meltzer (51), this was based on plasma 25(OH)D or

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1,25(OH)$_2$D concentrations. In the larger ((n=4638) 2021 study this was based on 25(OH)D only (39, 51). An increased risk of testing positive with lower category of vitamin D status (values below versus above 50 nmol/L (51) and below 50 nmol/L versus ≥ 100 nmol/L (39)) was reported in both studies. In subgroup analyses by ethnicity and controlling for a range of confounders and co-morbidities as well as time since last 25(OH)D test, Meltzer (39) reported an increased risk of infection (incidence rate ratio [IRR] 2.55 [95% CI, 1.26-5.15) in African Americans with a 25(OH)D below 50 nmol/ compared to those with a concentration over 100 nmol/L (<20 vs >40 ng/mL). The relationship between the COVID-19 IRR and 25(OH)D was non-linear and non-significant for the category 50-75 nmol/L compared to ≥ 100 nmol/L. This association with 25(OH)D was not found in white counterparts. The results from Kaufman and Meltzer suggest that there may be an interaction between ethnicity, vitamin D status and COVID-19 risk, but can also be determined by other factors that differ by ethnic group as outlined above. Such associations between COVID infection risk and vitamin D status may be lost in those reports that applied statistical adjustment for ethnicity (50), since at temperate climates, vitamin D status differs by ethnic group. Another study (Israel; subtropical region) reported an increased odds ratio for infection and hospitalization with COVID-19 amongst patients who had a plasma 25(OH)D below 75 nmol/L tested before the COVID-19 outbreak (52). In this study, it was unclear how long before the outbreak and in which season this prior test of 25(OH)D was done. Both Kaufman and Merzon (46, 52) did not correct for body composition, nor provided data whether treatment of vitamin D deficiency was initiated after testing, a factor considered in the 2 studies by Meltzer (39, 51).

There are several limitations to these prospective population-based studies and the use of medical records. Changes in recommendations for vitamin D intake and testing for and correction of deficiency may have resulted in secular trends in population vitamin D status. In the UK, population vitamin D status did however not substantially change after the 2016 revised guidance (https://www.gov.uk/government/collections/national-diet-and-nutrition-survey). Although vitamin D status is known to track within a person, it is strongly influenced by season. In temperate climates, like the UK, population vitamin D status typically cycles with the seasons, with a nadir in March and a peak in September (53). The nadir thus coincides with the peak of many respiratory viral infections, but also other factors play a role, including meteorological factors (temperature, UV index, humidity) influencing virus survival and time spent indoors (54, 55). It may therefore be reasonable to assume that vitamin D status at the time of viral exposure may be the more relevant measure than a year average or season adjusted value. Another study, relating the severity of the COVID outbreak with latitude and season also suggested a role of vitamin D status (56, 57). However, the subsequent spread

of the virus across all climate zones and the resurge of COVID prevalence in September 2020 and summer 2021 at Northern temperate latitudes, does not appear to strongly support this hypothesis. Data from population studies, such as the Biobank studies (44, 49, 50), are further limited by the fact that those typically at increased risk of being exposed or developing severe COVID-19 symptoms (i.e. ethnic minority groups and older frail people) are often underrepresented in population surveys (45, 48), while in data sets based on medical records, individuals with underlying health conditions may be overrepresented. In addition, in clinical data sets that are restricted to patients with a prior biochemical test of 25(OH)D, individuals with an increased risk of deficiency and receiving treatment are expected to be overrepresented. Changes in vitamin D status following testing and treatment also need to be considered. Notwithstanding, generating 'optimal' data to assess the protective role of vitamin D status would require near-impossible intense surveillance and sampling of large cohorts of people potentially acquiring the infection.

Findings of the first small, open label vitamin D intervention trial (n=50 intervention; n=26 control group) with hospitalised COVID-19 patients in Spain (diagnosed by positive PCR test and radiographic evidence of vital pneumonia) was recently published (18). In this study, which was a sub study COVIDIOL cohort, an intermediate high oral dose of calcifediol (the pharmaceutical form of 25(OH)D) at hospitalisation and at regular intervals thereafter was provided. The control group received standard medical care without vitamin D. In the vitamin D group, the risk of ICU admission was significantly reduced (OR 0.02 [95%CI 0.002-0.17]), but this was based 1 patient in the intervention group and 13 in the control group requiring ICU treatment. In this study a range of prognostic indices and risk factors for the development of severe symptoms were investigated. Compared to the intervention group, there was a higher prevalence of potential risk factors for the development of severe COVID in the control group (hypertension: 24 vs 58%, P=0.002; diabetes mellitus 6 vs 19%; P=0.08). After correction for these potential confounding factors, differences in the OR remained significant (OR 0.03 [95%CI 0.003-0.25]). Baseline and post supplementation vitamin D status was not assessed and potential confounding by body composition was not considered. Differences in deaths were also investigated and were not significant. However, interpretation of this outcome was hindered by the design the study, by which supplementation was stopped on admission to ICU. Nogues (20) reported a second sub study from the COVIDIOL cohort including a larger data set (n=447 intervention; n=391 control group). Interventions were identical but in this sub study, supplementation was continued after ICU admission. Baseline 25(OH)D was 32.5 [IQR 20-55] nmol/L. Co-morbidities were well balanced, except for a slightly lower baseline 25(OH)D concentration in the

control group. This study also showed a reduced risk of ICU admission with and without adjustments for confounders, which included baseline 25(OH)D (confounder adjusted OR 0.13 [95%CI 0.07-0.23]). Mortality was significantly reduced in the calcifediol supplemented group (confounder adjusted OR 0.21 [95%CI 0.10-0.43]). A randomised placebo-controlled vitamin D intervention trial in Brazil (n=120 intervention; n=120 placebo) with hospitalised COVID-19 patients (diagnosed by a positive PCR test) a single dose of 200,000 IU D_3, administered 1.4 days after admission and 10.3 days after onset of symptoms. Mean baseline 25(OH)D was 52 ± 9.1 nmol/L. This trial did not result in a reduction in length of hospitalisation, in-hospital mortality, risk of ICU admission or requiring mechanical ventilation (19). Rastogi (58) investigated the 21-day SARS-CoV-2 clearance rate in mildly or asymptomatic individuals with a 25(OH)D < 50 nmol/L (median baseline concentration < 25 nmol/L). Supplementation was open label and individually tailored to achieve a 25(OH) concentration over 50 nmol/L. They reported a higher proportion of patients that was SARS-CoV-2 negative after 21 days in the supplemented group (n=10 of 16; 62.5%) versus the placebo group (n=5 of 24; 20.8%), although the mean duration to SARS-CoV-2 negativety was not different between groups. No data were presented on the severity of symptoms or length of hospitalisation and no data on risk factors.

Only in the study by Murai, the time from onset of COVID symptoms was reported (10.3 ± 4.3 days); Nogues (20), Entrenas Castillo (18).and Murai (19) reported time from hospitalisation to supplementation (0, 0 and 1.4 (0.9 days) days, respectively). Considering the potential multifactorial role of vitamin D (and thus status and supplementation) in different stages and aspects of the response to viral infection and subsequent development of symptoms, time since infection and development of (severe) symptoms relative to the start of supplementation as well as baseline 25(OH)D concentrations may be important factors to consider in the evaluation of the effect of interventions. This is supported by secondary outcomes reported by Nogues (20). They found that when mortality rates were considered including both patients that initiated calcifediol treatment at hospitalisation (n=447) and those that first received this at ICU admission (n=53), the adjusted mortality OR (0.52 [95%CI 0.27-0.99]) was higher than when only patients were considered that initiated treatment at admission. The authors speculated that supplementation is more effective if initiated before the development of ARDS.

Not randomised, but an audit of standard care in a French nursing home found that residents that had received regular 2-3 monthly vitamin D supplementation (oral 80,000IU as a bolus) within 1 month before or 1 week after SARS-CoV-2 virus infection, had a less severe disease course and lower mortality (59). Similarly, an audit of vitamin D supplementation in frail hospitalised COVID-19 patients, showed a lower mortality risk in those that who had received regular vitamin D

supplementation preceding infection and in those supplemented directly after testing positive (both 80,000-100,000 IU as a bolus) compared to those that did not receive vitamin D supplementation (60).

Upper respiratory tract infections and vitamin D status and supplementation

Observational studies have shown that vitamin D deficiency may predispose to increased risk of viral acute respiratory tract infections (ARTI). Findings of the effect of vitamin D supplementation on the risk of preventing ARTIs are conflicting. Meta-analyses of RCTs and recent RCTs indicate that daily supplementation (intakes of 400 to 1000 IU/day) has a small protective effect (10, 11, 14, 15, 61). No protective effect was found with less frequent (weekly or less or after a bolus) administration. Many of the studies were conducted in populations with pre-existing respiratory diseases and in children. The most recent and largest meta-analyses found no interaction with 25(OH)D concentration at baseline (61), whereas in an earlier individual participant data meta-analyses, a stronger protective effect was found in subgroups with baseline vitamin D deficiency (< 25 nmol/L)(11, 62). The two UK Scientific Advisory Committee on Nutrition (SACN) rapid reviews on vitamin D and acute respiratory tract infections concluded that there is evidence of a small beneficial effect of vitamin D supplementation with intakes of 400 to 1000 IU/day, but that sufficient evidence is only available for children 1-16 years (https://www.gov.uk/government/publications/sacn-rapid-review-vitamin-d-and-acute-respiratory-tract-infections). A recent study in long-term care residents, with ~ 1/3 of participants with a baseline 25(OH)D <50 nmol/L, showed a significant protective effect (Odds ratio 0.67) with high dose monthly supplementation (100,000 IU per month). However in this study, consistent with other reports with high dose bolus vitamin D supplementation, an increased risk of falling was observed (13).

Evidence from a large multi-centre observational study in infants hospitalized for bronchiolitis suggests that vitamin D status is associated with the severity of respiratory disease. This study showed that the percentage of hospitalized children that proceeded to need intensive care treatment was almost twice as high in those with a 25(OH)D <50 nmol/L compared to those with a concentration >75 nmol/L (22 vs 12%) (63). Vitamin D intervention studies in children with pneumonia have however not shown a reduction of length of recovery and other disease outcomes (63).

Mechanistic studies support a role of vitamin D and its metabolites and vitamin D binding protein (DBP) on immune function and pulmonary health, which are summarised below. The contrasting findings between observational, mechanistic and intervention studies suggest that many other factors

play a role; the beneficial effects of vitamin D may be limited to specific subgroups, the alterations in vitamin D metabolism with disease processes may influence its function and/or other drivers of the immune and inflammatory response may be predominant, particularly in severe illness.

Summary of interactions of vitamin D metabolites and vitamin D binding protein with respiratory tract infections and immune function

The effect of vitamin D and DBP on immune function and pulmonary health has been described in in-vitro, ex-vivo and animal models and in human health (64). It is considered to be multi-factorial and involves both the innate and adaptive immune function (for reviews: (10, 64, 65)). Laboratory studies indicate that the active metabolite 1,25 dihydroxy vitamin D (1,25(OH)$_2$D) modulates the expression of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV, including SARS-CoV-2 and may thus modulate viral entry and infection (10, 56). To date it is unclear what the importance of this mechanism is. Vitamin D metabolites and DBP appear to play an important role in the immune and inflammatory response and hence disease severity san the development of immunity. It may also be hypothesised that vitamin D status may modulate the response to vaccination. Many of the cells of the immune system and those with a barrier function, express vitamin D receptors (VDRs) and CYP27B1, the enzyme that hydroxylates 25(OH)D into 1,25(OH)$_2$D. This locally produced 1,25(OH)$_2$D activates VDRs for autocrine and paracrine functions. It stimulates the expression of the antimicrobial function of cathelicidin which modulates the chemokine and cytokine response and stimulates the chemotaxis of neutrophils, monocytes and T-cells, thus promoting the clearance of respiratory pathogens (10, 64-66). Further, 25(OH)D and 1,25(OH)$_2$D stimulate autophagic encapsulation of viral particles promoting lysosomal degradation and antigen presentation (65). The role of vitamin D deficiency and supplementation on lymphocyte differentiation and apoptosis remains unclear (67, 68), but considering that severe illness with COVID-19 is characterised by inadequate T-cell responses (1, 69), it may be expected that the effects of vitamin D metabolites on immune function with severe COVID may be altered. It may therefore be speculated that vitamin D status may be of particular importance in earlier stages and the progression of the disease preventing the development a cytokine storm, found in patients with a severe disease course of COVID-19 (10, 64). Vitamin D deficiency has also have been linked to increased risk of the development of endothelial dysfunction and cardiovascular complications, frequently observed in patients hospitalised with COVID-19. Although no direct casual evidence is available, mechanistic studies suggest that deficiency or reduced VDR activation leads to overexpression of the renin- angiotensin aldosterone system (RAAS), hypertension and increased

thrombogenicity (65). This may influence the effects SARS-CoV-2 infection and its interaction with the ACE2 receptor, suggested to lead to dysregulation of RAAS (65, 70).

Summary of Vitamin D metabolism

Vitamin D metabolism

Vitamin D is synthesized in the skin after sunshine exposure and taken up into the lymph system. In temperate climates this only occurs during spring and summer months, whereas at latitudes < 30º North and South this can take place throughout the year. Oral vitamin D is rapidly and efficiently absorbed from the intestine incorporated in chylomicrons. Vitamin D from both supply routes is transported to the liver, but part of it may be taken up by fat tissue. In the liver, vitamin D is converted to 25(OH)D (Figure 1). Despite the efficient conversion (~80% at first passage with normal liver function), it takes several days to weeks to correct vitamin D deficiency unless high (bolus) dosages are given, particularly in severely deficient patients with a high BMI. This is thought to be due to the uptake of vitamin D by fat cells. Oral supplementation with 25(OH)D (i.e. calcifediol), at present only available on prescription, leads to a faster (with an increase already detectable within a few hours after administration) and proportionally higher increase in plasma 25(OH)D (71).

A further conversion into the active metabolite $1,25(OH)_2D$ is required and this occurs in the kidney for systemic effects. Local conversion takes place in many other tissues for auto-and paracrine effects, including the lung and cells of the immune system. The regulation of $1,25(OH)_2D$ production in the kidney is predominantly under control of parathyroid hormone (PTH), $1,25(OH)_2D$ itself, Fibroblast Growth Factor 23 (FGF23) and several other factors including sex hormones (reviewed in (71)). The extra-renal production is not under the control of these factors, except for FGF23. Instead, its regulation is thought to be tissue specific and is only partly understood. In immune cells, the regulation of $1,25(OH)_2D$ production is partly influenced by inflammatory factors and cytokines (reviewed in (10, 64, 72)) (Figure 1).

Generally, there is no or a poor correlation between plasma concentrations of 25(OH)D and $1,25(OH)_2D$. The concentration below which 25(OH)D becomes rate limiting for $1,25(OH)_2D$ production is not well established and also depends on other factors. It is generally assumed that when 25(OH)D falls below 15nmol/L, plasma $1,25(OH)_2D$ is reduced (71). A meta-analyses of supplementation studies however showed that post-supplementation $1,25(OH)_2D$ concentrations also

increased when baseline 25(OH)D concentrations were above 15-20 nmol/L (73). It is unclear whether at lower 25(OH)D concentrations the balance between renal and extra-renal 25(OH)D availability and tissue uptake is altered. In the kidney, internalization of 25(OH)D, bound to its binding protein is through an active megalin-cubulin receptor mediated mechanism. It may therefore be assumed that renal uptake takes place against the concentration gradient, partly overcoming the effects of low plasma 25(OH)D availability. In most other tissues, including those pertaining to the immune system, a receptor mediated internalization mechanism has not been demonstrated. According to the free hormone theory, cellular uptake in these extra-renal tissues is thought to be concentration dependent and thus is reduced when 25(OH)D is low (see further below).

The role of vitamin D binding protein in vitamin D metabolism

The majority of vitamin D and its metabolites circulate in plasma bound to DBP (~85 – 90%) and to a lesser extent and with a lower binding affinity to albumin. Less than 1% circulates in its free form (71). In healthy people, the free 25(OH)D concentration is highly correlated to total 25(OH)D and accordingly, the free: total 25(OH)D ratio is stable throughout the physiological ranges of 25(OH)D (74). In some physiological and pathological conditions, the free 25(OH)D fraction is altered and this is thought to be predominantly a result of changes in the concentrations of DBP (74). DBP binding of vitamin D metabolites has several functions: to prolong half-life and to facilitate cellular internalization of vitamin D metabolites through the megalin-cubulin receptor pathway. The megalin-cubulin receptor is expressed in a number of other tissues and is not specific for the DBP-vitamin D complex. Internalization of vitamin D metabolites through this pathway has to date only been shown in renal and muscle tissue and potentially in the mammary gland. Other tissues, including those pertaining to the immune system are thought to be mostly dependent on the internalization of the free fraction. However, other internalization mechanism for 25(OH)D and $1,25(OH)_2D$ have been proposed and DBP also plays an important role in the delivery and distribution of compounds to all tissues (75).

The megalin-cubilin mediated internalization of the DBP-25(OH)D complex is thought to be the predominant internalization route in the kidney and is also essential for renal reabsorption of the DBP complex and thus prevents urinary losses of both the protein and the associated vitamin D metabolites. A decrease in the expression of these receptors with renal impairment is associated with a decline in systemic $1,25(OH)_2D$ concentrations. It may be speculated that also a reduction of plasma DBP may

lead to a reduction in renal bioavailability of vitamin D metabolites reducing the substrate for production of systemic $1,25(OH)_2D$.

DBP binding protects against catabolism of vitamin D metabolites. As a consequence, in conditions with a decreased DBP concentration, although this has never been measured directly, it is expected that the bodily stores of 25(OH)D are more rapidly depleted and that the half-life of 25(OH)D and the active metabolite $1,25(OH)_2D$ decreases. This potentially explains the decrease in vitamin D status during acute illness and the frequently observed poor vitamin D status in ICU patients, even in those that do not have the traditional risk factors and may have an adequate vitamin D intake. These mechanisms may also partly explain the low and decline in $1,25(OH)_2D$ concentrations observed in many ICU patients as set out in the next sections.

DBP further fulfils several other functions in the immune system and in response to inflammation and tissue damage as summarised below (71, 75, 76).

Regulation of the concentration and production of vitamin D binding protein

Vitamin D binding protein is mainly produced in the liver, although the gene and protein are also expressed in very low concentrations in other tissues, including monocytes (77). It has three domains. The 'A' domain binds vitamin D metabolites and the B and C domains actin and this can occur simultaneously (76). The estimated daily production of DBP is about 700–900 mg/d for an adult (10 mg/kg/d). The plasma concentration of DBP in healthy people is in the μmolar range (~6 μmol/L or 300 ml/L) and is remarkably stable throughout the life-course. After acute depletion, for example after trauma or plasma exchange, DBP returns to baseline values after several days (78). The reported mean plasma concentrations in healthy populations vary between 200 and 600 mg/L. These differences are probably mostly related to assay differences and lack of standardization. Some (monoclonal) assays report lower values for specific population groups due to their incomplete quantitation of specific genotypes of DBP (79).

Similar to albumin, 40% of DBP is intravascular and 60% is distributed in the interstitial space of various organs (primarily muscle, adipose tissue, connective tissue and skin). It is also present in bronchoalveolar, amniotic, cerebral and seminal fluid, breast milk and saliva and bound to the cell surface of many cell types, including neutrophils (76, 77, 80).

In humans, exposure to oestrogens increases serum DBP but androgens have no effects. Vitamin D status (including deficiency and excess) and supplementation have no effect on serum DBP concentration. In vitro-models showed that dexamethasone, interleukine-6 (IL-6) and tumor necrosis factor alpha (TNFα) stimulate, while transforming growth factor beta (TGFβ) inhibits its production (81). Accordingly, DBP hepatic production was reported to increase in trauma patients (82). Although acute inflammation decreases plasma DBP concentrations, in states of chronic grade inflammation such as in obesity and rheumatoid arthritis, comparable or slightly higher DBP concentrations are reported, suggesting that increased hepatic production compensates for the potential higher degradation rate of DBP.

Decreased serum DBP concentrations are found in patients with liver cirrhosis, with protein-energy restriction and malnutrition, peritoneal dialysis, nephrotic syndrome and with a variety of other kidney diseases with proteinuria and renal loss of DBP (74, 76, 83, 84). Plasma DBP is also decreased in conditions associated with cell lysis and the release of intracellular actin into the bloodstream such as during infections or trauma (85-87). This decline in DBP reflects its role as actin scavenger protein (76, 83, 88).

The role of vitamin D binding protein and vitamin D in actin scavenging and coagulation

Actin is the most abundant intracellular protein in any organism. During tissue injury actin is released into extracellular fluids. Intra-cellular actin exists in two states: monomeric globular actin (G-actin) or G-actin polymerized into filaments (F-actin) (72). The process of polymerization and depolymerization is dynamic and highly regulated by actin binding proteins. When released into the extracellular space, actin escapes normal intracellular regulatory mechanisms and the protein will form F-actin filaments. In animal models, extracellular F-actin filaments have been shown to alter the coagulation and fibrinolytic systems leading to occlusion and damage of the microcirculation, particularly in the lung (72). Actin scavenging by DBP, together with ghelsolin plays an important role in the clearance of actin from the circulation and the prevention of formation of actin filaments. In addition DBP, particularly when bound to actin, has a regulatory function in neutrophil chemotaxis and after conversion to macrophage activating factor, in macrophage activation (10, 72). The function of DBP as a neutrophil chemotactic cofactor is modulated by $1,25(OH)_2$D-DBP binding (72). Much of the mechanisms are still poorly understood (10, 72, 77, 89).

Upon DBP binding of actin, the complex is rapidly catabolized, decreasing DBP plasma half-life from 1.7-3 days to 30 min (76, 83, 88). Bound vitamin D metabolites are released and although they may rapidly re-associate with another DBP molecule, the free fraction of vitamin D metabolites increases. This may be a beneficial response to infection, increasing the availability of vitamin D metabolites for passive cellular internalization, which may particularly increase the uptake into extra-renal tissues.

Strategies to improve DBP plasma concentrations in patients through stimulation of endogenous production or intra-venous administration have not been tested in humans. Administration of (human) DBP to healthy animals was not associated with toxic effects, except the formation of antibodies against the human form of DBP (90). In-vitro models have however shown that exposure to the actin-DBP complex causes inflammation and cell death (91). The safety profile may therefore depend on the presence of actin in the extracellular space. Caution therefore is warranted with strategies to rapidly and extensively increase the DBP concentration in the presence of extracellular actin as this may increase the inflammatory response (72).

Vitamin D status and metabolism in acute and critically ill patients

Vitamin D deficiency is commonly found in critically ill patients of all ages (63, 85, 87, 92-96) and is associated with increased mortality and morbidity (16, 17). It is unclear whether vitamin D deficiency in these patients is a marker of (pre-existing) poor health, low supply prior to hospitalisation (due to limited opportunities for spending time outdoors and/or low dietary intake), develops as a result of altered metabolism or whether low tissue availability plays a role in the disease process. In many, but not all studies a decrease in 25(OH)D is reported over the course of hospitalization (16, 85, 87, 97-101). Also a lower plasma $1,25(OH)_2$ D concentration compared to matched controls and a decrease in $1,25(OH)_2$ D is reported in critically ill patients and in patients undergoing major surgery (16, 95, 97, 102-105).

In a longitudinal observational study, Ney (16) showed that pre-operative $1,25(OH)_2$ D concentrations in patients undergoing major cardiac surgery was a negative predictor of post-operative organ failure, sepsis, mortality and prolonged hospital stay, whereas pre-operative 25(OH)D was not predictive. Although the relationship with post-operative $1,25(OH)_2D$ with health outcomes was not reported, pre and post-operative concentrations seemed to be correlated and those with low pre-operative values had a further decline in $1,25(OH)_2D$. This parallels findings of a study in ICU patients treated with a high

bolus dose of vitamin D. Post-hoc analyses showed that plasma the $1,25(OH)_2D$ concentration measured 3 days after vitamin D administration, not $25(OH)D$ was predictive of 28d survival (99). This indicates that renal activation of $25(OH)D$ into (systemic) $1,25(OH)_2D$ and maintenance of plasma $1,25(OH)_2D$ concentrations play a key role.

Several mechanisms provide potential explanations (for a summary see Figure 1). Renal impairment and AKI are highly prevalent in ICU patients. This is also found in patients with severe COVID-19 symptoms. Renal damage reduces the capacity to convert $25(OH)D$ into $1,25(OH)_2D$ (106, 107) and leads to renal losses of vitamin D metabolites bound to DBP and albumin (87, 102). Further, animal models of sepsis show that renal $1,25(OH)_2D$ production may have decreased as a result of decline in insulin growth factor 1 (IGF-1; known to stimulate $1,25(OH)_2D$ production), despite an increase in PTH, commonly observed in sepsis. Catabolism may be expected to be increased due to an increase in FGF23 (known to decrease the half-life of $1,25(OH)_2D$). Finally, the decline in DBP observed with acute and critical illness (see further below) is expected to be associated with an increase in the free fraction and therefore catabolism of vitamin D metabolites (71).

An alternative explanation for the decrease in $1,25(OH)_2D$ concentrations is a functional downregulation of the total concentration in order to maintain free $1,25(OH)_2D$ concentrations constant. This is observed in several studies conducted after surgery, where the free fractions of $25(OH)D$ and $1,25(OH)_2D$ remained constant in the presence of a decrease in DBP (108, 109). A longitudinal study in ICU patients however showed that the decline in $1,25(OH)_2D$ and $25(OH)D$ by far exceeded the decline in DBP, rendering the free fractions of these metabolites significantly lower than in healthy controls (105).

Severe trauma (e.g. hip fracture), major surgical procedures and severe illness (including septic shock, ARDS) leads to pronounced changes in DBP concentrations (85-88). Although not detailed in most reports, this should be assumed to reflect the actin-free DBP concentration, which is measured in most types of assays. Where total DBP is measured, the concentration has been reported to increase (88). In 2 longitudinal studies in ICU or patients with severe trauma, the total concentration or actin free DBP was shown to initially decrease, while the complexed DBP concentration increased. Subsequently, measured over the course of 7-10 days, actin free and actin bound DBP concentrations increased (82, 105). The plasma concentrations of DBP (either measured as total, actin-free and actin-bound) is reported to be a sensitive predictor of in hospital complications, including sepsis and respiratory distress and failure and of mortality (72, 80, 82, 88, 110-114). These data indicate that DBP actin

binding capacity and hepatic DBP production in severely ill patients plays an important role in survival. It has been hypothesized that when actin release exceeds DBP scavenging capacity, the formation of actin filaments leads to increased viscosity and increased risk of coagulation (80, 86, 105). Considering that DBP is also present in alveolar fluids, its involvement in the prevention and development of airway obstructions may be expected (77, 80), although the role of DBP and change in DBP concentrations with cell lysis and inflammation in extra-vascular fluids is mostly unknown.

Venous and arterial thromboembolic events are common in ICU patients and with severe COVID-19, affecting approximately 30% of cases admitted to intensive care and occur despite thromboprophylaxis (56). In pre-clinical studies vitamin D has been shown to have anti-thrombotic effects and there has been considerable interest in the effects of vitamin D on coagulation, but large intervention studies have failed to show an impact of vitamin D status or supplementation on the risks for thromboembolism or cardiovascular disease (10). This is possibly related to the earlier described reduced capacity to convert 25(OH)D into 1,25(OH)$_2$D in patients typically at increased risk and depletion of actin scavenging capacity of DBP and ghelsolin and the concomitant decrease in plasma albumin concentration, which are not influenced by vitamin D supplementation (106, 107).

Also other aspects of altered metabolism, tissue distribution and extracellular volume need to be considered in the interpretation of plasma concentrations of vitamin D metabolites, DBP and the potential of receptor activation. Treatment protocols of ICU and surgical patients (e.g. fluid load) may lead to significant haemodiluton; the distribution of compounds between the vascular and extra-vascular compartments may be changed; alterations of tissue uptake and receptor expression may modify sensitivity and changes of circadian rhythms (well known to play an important role in vitamin D metabolism and calcium and phosphate homeostasis (115)), may all lead to pronounced changes in plasma concentrations of any biochemical marker (116-118). All these factors and mechanisms may have implications for the interpretation of findings in ICU patients and potential treatment strategies.

Randomised controlled trials with vitamin D in ICU and acutely ill patients

There is a limited number of published RCTs in adults with administration of native vitamin D (104, 119-125), the pharmaceutical form of 25(OH)D (calcifediol) or 25(OH)D (105) or 1,25(OH)$_2$D (126) in critically ill patients. In the majority of studies, vitamin D or 25(OH)D was given as either a high bolus, or a loading dosage followed by lower maintenance doses. This strategy is chosen when time is critical

and has been shown to lead to a rapid correction of vitamin D deficiency (71, 105). These trails were designed (and powered) for different primary and secondary outcomes and the majority were of small size (n<100) and differed in study population. These trials reported conflicting results. Several meta-analyses were conducted and focused on hard clinical end points. Jointly, meta-analyses of these trials showed no effect on length of hospital or ICU stay and/or requirement for mechanical ventilation (127-130). No effect on mortality (total 28-day or split by mortality in hospital or ICU; mortality after 7, 28-30, 84 days and 6 months) was reported in 3 of the meta-analyses (128-130), while Putzu (127) reported a lower odds ratio (0.70 CI: 0.50-0.98) for total mortality (as recorded at the last day of data collection of an individual study) with vitamin D supplementation. The largest, recent multi-centre RCT (n= 1360) (123) was only included in the meta-analyses conducted by Lan (128). This RCT recruited vitamin D deficient (defined as 25(OH)D < 50 nmol/L) patients at high risk of death or lung injury and a bolus of vitamin D (540,000 IU D_3) was given within 12 hours after ICU admission. This trial found no effect on 28 or 90-day mortality, days on ventilation and length of stay in hospital or other health care facilities and none of the wide range of other health outcomes and measurements (which included the percentage of patients that developed ARDS), reached statistical significance. The trial, originally designed to recruit 3000 patients, was stopped on basis of interim analyses predicting no effect of treatment.

Trials varied in form, dosages, frequency and length of administration of vitamin D or its metabolite. The route of administration was oral, intra-venous or intramuscular. Considering the differences in pharmaco-kinetic profiles and bio-availability as influenced by the form of vitamin D (native or its metabolite(s)), dosage, frequency and length of administration and route of administration (reviewed in (71)), this may be expected to have influenced the results of individual trials. The majority of studies administered a bolus or provided vitamin D for a short length of time. Two meta-analyses analysed the influence of factors affecting the pharmaco-kinetic profiles. In these, no significant interaction was found between outcomes and route, length and dose of administration (128, 130). However, the validity of outcomes reported after more than 5 times the half-life of either 25(OH)D or 1,25 (OH)$_2$D is questionable (25(OH)D: ~ 2-3 weeks; 1,25(OH)$_2$D: ~ 5 hours), unless these were reported as cumulative data. In addition, administration of bolus dosages, although leading to a rapid increase in 25(OH)D, has a disadvantageous pharmaco-kinetic profile as set out below in the section 'Symptoms and correction of vitamin D deficiency'. Studies designed to initially rapidly correct vitamin D deficiency, followed by a maintenance dose schedule may be more suitable to evaluate the effect of vitamin D administration in ICU patients.

Most of the intervention studies in ICU patients also showed no effect on plasma concentrations of markers of immune function and inflammatory or pro-inflammatory markers such as cathelicidin, interleukin 6 (IL-6), C-reactive protein and procalcitonin, measured 6 hours to 14 days after (the start of) vitamin D administration (105, 119, 121, 123, 131). However, Leaf (126) demonstrated that $1,25(OH)_2D$ administration increased the leucocyte mRNA expression of cathelicidin and interleukin-10 in sepsis patients. Quraishi (120), also in a study with sepsis patients given enteral vitamin D (400,000IU as a bolus), found an increase in plasma cathelicidin and a decrease in IL-6 after 5 days. This study also reported a range of other inflammation markers (e.g. C-reactive protein, TNF-α and IFN-γ), which were unchanged. This may potentially reflect that during severe illness, other drivers of inflammation have a predominant effect.

The dose-response to vitamin D administration in ICU patients is poorly characterized and not formally subjected to meta-analyses. Studies have shown that the response to vitamin D and 25(OH)D given both orally and intravenously to ICU patients is blunted compared to healthy people (105). This is likely a result of impaired hepatic conversion, increased renal losses and a more rapid catabolism. In generally healthy older people, vitamin D supplementation at high bolus dosages appears not to have beneficial effects compared to lower daily or weekly dosages, but has a disadvantageous pharmaco-kinetic profile (71) and it may increase the propensity of falls (132) (133) (https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention and www.endocrinology.org/media/3593/nos_vitamin_d_and_bone_-health_in_adults_web.pdf). In addition, it may increase the risk of hypercalcemia and hypercalciuria (15). This appears to be a limited issue in ICU patients. Meta-analyses of the occurrence of hypercalcemia in RCTs in ICU patients showed no increased risk after supplementation with high dosages of vitamin D (127). Plasma $1,25(OH)_2D$ concentrations increased with supplementation and were well over the normal reference range in some patients (98, 104, 119, 126), but were not associated with hypercalcemia. This is in line with the observation that hypercalcemia is relatively uncommon and hypocalcaemia is frequently observed in ICU patients (35, 134). A decrease in total calcium is thought to be partly an adaptive response to maintain the biologically active fraction, ionized calcium, constant in the presence of a decrease in plasma binding proteins, the concentrations of which decrease with acute and critical illness. However, also the ionized calcium concentration often is below normal ranges with sepsis and other acute inflammatory illnesses. Although mortality rates are higher in patients with sepsis with hypocalcaemia, replacement therapy is not associated with improved outcomes (134).

Current research investigates the effects of administration of the pharmaceutical form of 25(OH)D, calcifediol and active vitamin D or analogues in critically ill patients (105, 135, 136). With these forms, the consequences of impaired absorption and activation of native vitamin D may be reduced. Patients with intestinal malfunction, fat malabsorption and poor liver function may benefit more from supplementation with 25(OH)D. The absorption of this form does not depend on fat absorption or the formation of chylomicrons, does not require hepatic hydroxylation and leads to a faster and proportionally higher increment in plasma 25(OH)D per unit given compared to vitamin D (71, 137-140). In addition, limited evidence in CKD stage 2-4 patients has shown that administration of the slow release formulation of 25(OH)D is not associated with an increase in FGF23 (141, 142), observed with higher dosages of oral vitamin D (143). This may be of particular importance for severely ill patients, since in many, production of renal and possibly extra-renal $1,25(OH)_2D$ is impeded due to renal impairment and increased catabolism as described in the previous section. To date, the availability of this form is however limited. In patients with renal impairment and AKI, administration of active vitamin D or analogues may be considered, similar to those for patients with CKD. A combination with native vitamin D to ensure tissue availability of 25(OH)D for extra-renal hydroxylation may be beneficial in this group (135, 144).

Together, the contrasting findings between observational, mechanistic and intervention studies suggest that many other factors than vitamin D status and intake play a role. The extensive alterations vitamin D metabolism with disease processes may influence its function. With acute and severe illness, other drivers and regulatory factors of the immune and inflammatory response may be predominant and may be determined by alterations in organ function and tissue damage.

Implications for practice

Prevention of vitamin D deficiency and population guidelines

Thresholds for vitamin D deficiency for the general population differ between advisory bodies, but most define plasma 25(OH)D values below 25-30 nmol/L as deficient (reviewed in (23-25, 145)). There is considerable variation between health authorities in the definition and thresholds or ranges of 25(OH)D concentration that encompasses vitamin D sufficiency or define target ranges of 25(OH)D on which to base dietary recommendations (25, 145). Recommended 25(OH)D target concentrations and

thresholds for deficiency for specific patient groups and clinical management may be higher than for generally healthy people (reviewed in (25, 145)).

The threshold for deficiency is the concentration of 25(OH)D below which the risk of disease increases. This is predominantly based on health outcomes related to calcium metabolism and musculoskeletal health, but in some guidelines also other health outcomes are considered. Although vitamin D deficiency is associated with many other health outcomes, discordant findings between observational studies and RCTs of vitamin D treatment are reported. An overview is beyond the scope of this manuscript and reviewed elsewhere (26-28).

Population guidelines for dietary vitamin D intakes are partly based on the required intakes to prevent vitamin D deficiency or to achieve pre-defined target ranges of 25(OH)D or sufficiency. Also evidence from RCTs and other research designs linking vitamin D intake and status to health outcomes are considered. Dietary reference values (DRV) or equivalents, defined by different public health institutes vary as a consequence of differences in the defined threshold for deficiency, sufficiency or target values for 25(OH)D (reviewed in (25, 145)). Guidelines for dietary intakes and supplementation also depend on age group, physiological state, risk factors (as per below) and in some countries, on season. An overview of population guidelines from health authorities across the world was recently published by Bouillon (145). In most guidelines it is acknowledged that the majority of people do not consume sufficient vitamin D through diet alone and thus supplementation is needed to meet requirements. In most guidance, a contribution of cutaneous synthesized vitamin D is taken into account in the formulation of recommendations of dietary requirements. Advice on sunshine exposure to maintain vitamin D status is generally not provided in view of the variability in the response to cutaneous exposure and the risk of skin damage.

In temperate climates, supplementation is recommended during winter months. Supplementation throughout the year is recommended for pregnant women and people at increased risk of deficiency. At risk are population groups with a dark skin tone, obesity and people with limited skin exposure to the sun (i.e. with a habitual dress-style that covers most of the body, frequent sunscreen use, people with limited access to the outdoors, e.g. when mobility is limited or living in residential care and during illness). It seems appropriate to also apply this recommendation to those that are in prolonged self-isolation and therefore mostly indoors. Screening of vitamin D status is not recommended for the general population. This is limited to individuals at increased risk of deficiency (as described above) or who are symptomatic (15, 23, 145).

Symptoms and correction of vitamin D deficiency

The main manifestation of severe vitamin D deficiency is osteomalacia in adults and rickets in children. It is associated with secondary hyperparathyroidism, bone loss, muscle weakness, falls and fragility fractures and in children, also cardiomyopathy and hypocalcemia. Clinical symptoms of vitamin D deficiency are non-specific and include generalized muscle, joint and bone pain and hyperalgesia, fatigue, muscle weakness, especially of the extremities and pelvic region manifesting in difficulties in rising from a sitting or squatting position or a waddling gait (146) (https://www.endocrinology.org/media/3593/nos_vitamin_d_and_bone_-health_in_adults_web.pdf).

When vitamin D deficiency is present (ideally assessed on basis of plasma 25(OH)D), or strongly suspected on the basis of clinical symptoms in combination with primary risk factors (see previous sections), higher intakes than daily population requirements, are required. Recommendations for dosage regimens depend on local health authorities and specific patient characteristics and target ranges for 25(OH)D (see section below). In the UK, an intake of 800 IU/d is advised when vitamin D deficiency is mild and correction is not urgently required. This approach does not generally require clinical testing and management. When rapid correction of deficiency is needed, such as in patients with severe deficiency or with symptomatic disease, the recommended treatment regimen is based on fixed loading doses followed by maintenance therapy. Loading regimens aim to provide a total of approximately 300,000 IU given over a period of 6-10 weeks as weekly or daily split doses. Similarly, the US Endocrine Society recommends a loading dose of 3-400,000 IU given over 8 weeks (145, 147). Maintenance regimens recommend intakes of 800 to 2,000 IU daily (up to a maximum of 4,000 IU daily), given either daily or intermittently at a higher equivalent dose. Treatment with these higher dosage schedules should be monitored with appropriate clinical testing and management. Large loading dosages exceeding 60,000 IU given at once, should be avoided. (https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention and www.endocrinology.org/media/3593/nos_vitamin_d_and_bone_-health_in_adults_web.pdf)(145, 147) High bolus dosages are associated with an increased risk of falling in adults. In addition, higher dosages including when given as a bolus, have a different and potentially disadvantageous pharmaco-kinetic profile (71, 148); with a high bolus dose, the plasma concentration of 25(OH)D rapidly increases and there may also be a small increase in $1,25(OH)_2D$ (149). This is followed by an increase in catabolism through increased 24 hydroxylation. This is partly mediated through an increase in

FGF23 (133, 143, 150) and 1,25(OH)$_2$D itself (149, 151). This results in increased conversion into 24,25(OH)$_2$D and potentially other catabolic products from 25(OH)D and possibly vitamin D itself. Also, the rate of catabolism of 1,25(OH)$_2$D is expected to increase (133, 149, 151).

Guidelines for prevention and correction of vitamin D deficiency in specific patient groups.

Recommended intakes, 25(OH)D target concentrations and thresholds for deficiency for specific patient groups and clinical management may be higher than for generally healthy people (145). They consider altered supply or bio-availability, losses, increased metabolism and/or requirements or a combination of these factors. Little is known about the vitamin D requirements during acute or chronic illness. Even for chronic conditions that clearly affect vitamin D metabolism (such as renal (144) and hepatic disease (152-154)) or bioavailability (conditions affecting intestinal fat and/or vitamin D absorption such as with coeliac and inflammatory bowel disease (155, 156)), direct evidence on requirements is scarce. Also certain types of medication are associated with altered vitamin D metabolism, e.g. corticosteroids, anti-epileptic drugs and drugs inhibiting fat absorption (145, 147)(https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention), or increase dietary calcium requirements, such as medications reducing bone loss. With these conditions, specific patient management guidelines should be followed, where formulated (renal (144)(25); hepatic (152-154); coeliac (155); inflammatory bowel disease (156); osteoporosis (theros.org.uk)). Many guidelines recommend regular testing of vitamin D status and correction of deficiency if and as required with monitoring of side effects and until a target plasma concentration or range of 25(OH)D is reached. Dependent on the aspect of metabolism affected and severity or disease, guidelines may recommend prescribing native vitamin D, 25(OH)D or active vitamin D or their analogues (144, 152-154, 157-159).

Management of vitamin D status in people with acute and critical illness

Little is known about the vitamin D requirements during acute and critical illness or with inflammation (23, 136).

For patients with mild and short-term acute illnesses, such as during a mild disease course following infection with SARS-CoV-2 and/or during self-isolation, supplementation with vitamin D to prevent vitamin D deficiency according to population guidelines for groups with no or limited sun exposure is

appropriate (23, 145). In the presence of risk factors or symptoms of deficiency, testing of vitamin D status and correction of vitamin D deficiency is warranted, as described above.

There is no specific guidance to prevent vitamin D deficiency in severely ill patients (136). The standard formulations for enteral feeding contain 200-400 IU vitamin D per day and parenteral multivitamin preparations typically contain only 200 or 220 IU per day. This is below the population recommendations in the majority of countries. As outlined in previous sections, patients with acute and critical illness are often vitamin D deficient at admission and may have a rapid decline in vitamin D status, suggesting that vitamin D requirements are increased. This may be the result of altered bioavailability or metabolism, increased utilization and losses of $1,25(OH)_2D$ and $25(OH)D$ and medication use increasing catabolism, such as corticosteroids. The most recent update for critically ill patients recommends screening of patients for vitamin D deficiency and those with plasma $25(OH)D$ concentrations below 30 nmol/L to be supplemented with a single high dose of vitamin D_3 (500,000 IU) within a week after admission (160, 161). No guidance is available regarding monitoring, frequency of testing and maintenance therapy. Considering the likelihood of increased requirements, it seems reasonable to provide regular (daily or weekly) vitamin D supplementation similar to the maintenance schedules recommended for patients after correction of vitamin D deficiency, as described above with regular testing of plasma $25(OH)D$.

In consideration of underlying conditions and acute alterations in organ function with critical illness, the use of activated or partly activated vitamin D metabolites may be considered. Current research investigates the effects of administration of $25(OH)D$ and active vitamin D in critically ill patients, but this research is as yet not incorporated in guidelines.

Conclusions

No data are yet available demonstrating a causative link between low vitamin D status and susceptibility for COVID-19 or its disease course. Data from observation studies investigating the association between vitamin D status and risk of infection and/or developing severe symptoms are conflicting. Vitamin D deficiency is highly prevalent in patients hospitalised with COVID-19 and with other conditions, particularly those that are severely ill. This may be related to the presence of risk factors for vitamin D deficiency, associated with their general poor health status or increased catabolism and losses of $25(OH)D$ during disease. There are extensive alterations in vitamin D

metabolism with severe illness and inflammatory processes which may increase requirements of vitamin D. This needs consideration in the assessment of associations with disease risk and severity and in patient management. Although mechanistic studies show that vitamin D metabolites and DBP have a multi-factorial roles in pulmonary health, immune function and inflammatory response to viral infection and tissue damage, supplementation of ICU patients has so far however shown little effect. The contrasting findings between observational, mechanistic and intervention studies suggest that many other factors play a role. Alterations in vitamin D metabolism with disease processes may influence its function and/or other drivers of the immune and inflammatory response may be predominant. The effect may depend on when supplementation is initiated relative to the development of disease symptoms and progression to severe illness and the frequency of administration. Such data are not yet available. The beneficial effects of vitamin D may also be limited to specific subgroups.

There is some evidence that vitamin D supplementation decreases the risk of respiratory tract infections, particularly in children, although the risk reduction is moderate. No such evidence is yet available for the prevention or treatment of COVID-19. In view of the high prevalence of vitamin D deficiency, pro-actively applying current population and patient management guidelines to prevent and correct vitamin D deficiency with screening and monitoring of vitamin D status in individuals that are at increased risk, is appropriate.

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Figure 1: Determinants of the kinetics of vitamin D and potential changes with severe illness and treatment.

Blue arrows indicate metabolic pathways of vitamin D and vitamin D metabolites. Letters indicate hydroxylation enzymes A: CYP2R1; B: CYP27B1; C: CYP24A1. Changes associated with severe illness lead to pronounced changes supply, distribution, hepatic conversion, renal losses and metabolism due to changes in hydroxylation enzyme activity. Determinants of these changes are summarised. Conversion (A) of vitamin D into 25(OH)D maybe impaired and activation (B) of 25(OH)D into 1,25(OH)$_2$D may be decreased and catabolism (C) of 25(OH) D into 24,25(OH)$_2$D and 1,25(OH)$_2$D into1,24,25(OH)$_3$D and further downstream products may be increased. Metabolism may further be influenced by medication use. For further explanation, see text.

Vitamin D metabolism is further influenced by physiological factors and life stage including growth, pregnancy and ageing.

Abbreviations: 25(OH)D: 25 hydroxy vitamin D; 1,25(OH)$_2$D: 1,25 dihydroxy vitamin D; 24,25(OH)$_2$D: 24,25 dihydroxy vitamin D: PTH: parathyroid hormone; IGF-1: Insulin Growth Factor 1; FGF23: Fibroblast Growth Factor 23: DBP: vitamin D binding protein.

Determinants of Vitamin D kinetics and status / Potential changes with illness and treatment

Supply

UVB exposure
Vitamin D intake

Absorption from diet

↓ Opportunity UVB exposure
Dietary intake

↓ Intestinal function & absorption

Distribution, conversion, losses

Fat mass
Lean mass
Extracellular volume

Hepatic conversion rate

Renal function

↑ Fluid load

↓ Liver function

↑ Renal DBP and metabolite losses

Metabolism

Hormonal regulators (systemic):
PTH
$1,25(OH)_2D$
IGF-1
FGF23
Sex hormones

Renal function

Regulators (auto and paracrine):
Tissue specific factors including:
Inflammatory factors and cytokines
FGF23

DBP

Dietary factors:
Calcium, Phosphate

↓ $1,25(OH)_2D$
IGF-1

↑ FGF23

↓ Renal $1,25(OH)_2D$ production capacity

↑ Inflammatory factors and cytokines

↓ DBP

↓ Dietary intake and absorption calcium and phosphate

Vitamin D

Plasma

A

$25(OH)D$

B   C

$1,25(OH)_2D$ $24,25(OH)_2D$

C   C

catabolism

excretion