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Vitamin D Levels in COVID-19 Patients Admitted to Intensive Care

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Abstract

Background: Vitamin D has garnered much attention for its role in immune function, more specifically, it's conceivable link to the clinical severity of Covid-19 infections and therefore its potential application in prophylactic or therapeutic treatment. Vitamin D appears capable of inhibiting pulmonary inflammatory responses while enhancing innate defence mechanisms against respiratory pathogens with population-based studies showing an association between circulating vitamin D levels and lung function. We understand that infection with Sars-Cov-2 induces production of pro and anti-inflammatory cytokines, whilst Vitamin D downregulates production of pro-inflammatory Th1 cytokines including tumour necrosis factor and interferon Y, whilst increasing expression of anti-inflammatory cytokines by macrophages. Vitamin D is also involved in the renin-angiotensin system which is regulated by entry of the SARS-Cov-2 virus into cells via the ACE2 receptor, leading to cytokine storms, with subsequent fatal respiratory distress syndrome. The theoretical implications for Vitamin D status in the presentation of Covid-19 (the disease state of Sars-Cov-2) exist, yet data on its application is currently limited. Geographical variables depicting patterns between sun exposure, diet or Vit D status, and risk of death from Covid-19 have shown strong negative correlation. **Aim:** We aim to assess levels of Vitamin D deficiency in ICU patients who have tested positive for Sars-Cov-2 and who have exhibited respiratory symptoms. In this way, we hope to identify the possibility of Vitamin D as a significant contributing factor to disease progression in Covid patients. **Sample:** Male or Female patients of any age, who were admitted to the Intensive Care Unit exhibiting respiratory symptoms, with a positive Sars-Cov-2 PCR test, between 12/3/21 and 25/2/21. sample total: 79. **Results:** Testing was very inconsistent with only 67.1% having their Vitamin D levels checked. There was average delay in testing levels by 2 days. 64% of patients were found to be very deficient. **Conclusion:** This study highlights the strong correlation between Vitamin D status and severity of Covid-19 disease and thus demonstrates a po-

tential huge shortfall in the testing and treatment of this immunodeficiency as it relates to Covid-19. Based on recommendations of Vitamin D levels required for protection of this viral syndrome, as much as 100% of patients sampled with severe disease could be deficient in Vitamin D.

Keywords

Covid-19, Sars-Cov-2, Vitamin D, Viral Syndrome, Cytokine Storm

1. Background/Rationale

Vitamin D has garnered much attention for its role in immune function, more specifically, it's conceivable link to the clinical severity of Covid-19 infections and therefore its potential application in prophylactic or therapeutic treatment.

Unlike other vitamins, Vitamin D exists as a prohormone, and is produced predominately endogenously (90%) via the skin and kidneys by way of UBV light, while 10% is gained exogenously through diet.

In the liver, vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are converted into 25-hydroxyvitamin D2 (25[OH]D2) and 25-hydroxyvitamin D3 (25(OH]D3), respectively [1]. In the kidney, 25(OH)D is converted to its biologically active form 1,25-dihydroxyvitamin D (1,25[OH]2D) by 1α-hydroxylase. The serum level of 25(OH)D is used to determine vitamin D status and normally ranges between 30 - 100 ng/mL (75 - 250 nmol/L).

In addition to its known role in calcium metabolism, it has crucial functions in supporting endothelial barriers and innate and adaptive immunity [2]. The receptor which binds Vitamin D is present in B cells, T cells and antigen presenting cells, all of which are capable of self-synthesising the active Vitamin D metabolite. In this way, it modulates the immune system in an autocrine manner. Therefore, deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection [3].

Vitamin D appears capable of inhibiting pulmonary inflammatory responses while enhancing innate defence mechanisms against respiratory pathogens with population-based studies showing an association between circulating vitamin D levels and lung function [4].

This is highlighted in a meta-analysis including 10,933 participants in 25 randomised controlled trials showing an overall protective effect of vitamin D supplementation against acute respiratory tract infection (number needed to treat (NNT) = 33) [5]. The greatest benefit is seen in those receiving daily or weekly Vitamin D without additional boluses (NNT = 20), with the protective effects against acute respiratory tract infections strongest in those with profound Vitamin D deficiency at baseline (NNT = 4).

We understand that infection with Sars-Cov-2 induces production of pro and anti-inflammatory cytokines, whilst Vitamin D downregulates production of pro-inflammatory Th1 cytokines including tumour necrosis factor and inter-

feron Y, whilst increasing expression of anti-inflammatory cytokines by macrophages [6] [7] [8].

Vitamin D is also involved in the renin–angiotensin system [9] which is regulated by entry of the SARS-Cov-2 virus into cells via the ACE2 receptor, leading to cytokine storms, with subsequent fatal respiratory distress syndrome [10].

The theoretical implications for Vitamin D status in the presentation of Covid-19 (the disease state of Sars-Cov-2) exist, yet data on its application is currently limited. Geographical variables depicting patterns between sun exposure, diet or Vit D status, and risk of death from Covid-19 have shown strong negative correlation.

For countries in Europe, the probability of developing COVID-19, and of dying from it, is negatively correlated with mean population vitamin D status, with both probabilities reaching zero above about 75 nmol/L [11]. Supplementing this link, comparison between Covid-19 mortality and climate showed that, after adjusting for age, there was a 4.4% increase in mortality for each degree latitude north of 28 degrees [12]. However, certain confounding effects due to the influence of weather on pathogenicity of the virus should be considered when interpreting these results.

Further correlations can be drawn between peaks in seasonal influenza, given its prevalence in climates where sun exposure is limited and Vitamin D in the population at its lowest [13].

Vitamin D deficiency is a frequent biochemical observation amongst minority groups in Britain [14]. It is hypothesised that this goes at least in some way to explain increased mortality witnessed in BAME community due to Covid in the UK [15].

Numerous studies have explored the efficacy of Vitamin D supplementation in the critically unwell groups such as trials (with low bias) included in a 2017 meta-analysis [16]. The primary end point was mortality, with secondary end points being length of hospital stay, length of ICU stay, length of mechanical ventilation and adverse events.

Seven studies with a total of 716 patients were included in the analysis. Vitamin D administration was associated with significantly lower mortality compared with placebo (101/320 [32%] in the vitamin D group vs 123/307 [40%] in the placebo group; odds ratio, 0.70 [95% confidence interval, 0.50 to 0.98]; P = 0.04; I2 = 0%). However, no differences in secondary end points were found.

Since, however, a large prospective, double-blind, placebo-controlled trial (VIOLET) measuring the effects of administration of cholecalciferol to those who were Vitamin D deficient and requiring admission to ICU was performed. The publication demonstrated no significant benefit, where a large single dose was given at the time of admission to ICU [17]. Whilst this study failed to show any improvement in overall mortality in the critically ill as a population, there are a few important distinctions to make. Firstly, the sample is of those being

admitted to ICU for whatever reason, representing a broad array of pathologies, and the results may not be mirrored when assessing those with viral syndromes or specifically, Covid-19. Secondly, the method involved giving a single large dose of Cholecalciferol. As demonstrated in the large Meta-analysis examining the link between Vitamin D and respiratory tract infections [3], benefit was only seen with regular supplementation, with no recorded benefit when given as a bolus. Thirdly, it was given within 12 hours upon making the decision to admit to ICU. Therefore, this does not address the potential benefits of mitigating progression to a severe clinical state as given after the fact.

Part of the theory behind Vitamin D use in the treatment of Covid-19 is its therapeutic enhancement of the corticosteroid effect [18]. Researchers have demonstrated how it up regulates glucocorticoid receptors leading to increase T-cell apoptosis whilst synergistically improving corticosteroid effect on, and suppression of, cytokine production in peripheral monocytes [19] [20] [21].

In a 2020 RCT, the effect of calcifediol (25-Hydroxyvitamin D) treatment with standard therapy, versus standard therapy alone for patients hospitalized for COVID-19, was measured [22].

76 consecutive patients hospitalized with COVID-19 infection were included (evidenced by clinical picture, radiographic pattern of viral pneumonia and positive Sars-Cov-2 PCR test).

All patients received the same standard care (per hospital protocol) of hydroxychloroquine (400 mg every 12 h on the first day, and 200 mg every 12 h for the following 5 days), plus azithromycin (500 mg orally for 5 days.) Eligible patients through electronic randomization were allocated at a 2:1 ratio to receive oral calcifediol (0.532mg), or not. Subsequently, patients in the calcifediol treatment group continued with oral calcifediol (0.266 mg) on days 3 and 7, and then weekly until discharge or ICU admission.

Primary outcomes of effectiveness were mortality and rate of ICU admissions.

Interestingly, what they found was that of the 50 patients treated with calcifediol, one required admission to ICU (2%) while of the 26 untreated patients, 13 required admissions to ICU (50%) $p < 0.001$, OR 0.02 [0.002 - 0.17]. None of the treated patients died but 2 in the control did. This study shows promising results but is limited by its size and therefore highlights the need for larger trials to deliver more definitive conclusions.

Given its role in immune function and much of the preliminary data available, it encourages a hypothesis that Vitamin D deficiency increases susceptibility to infections and thus supplementation may improve outcome, with specific implications for Patients with Covid-19. Strong evidence in support of this comes from a large observational analysis from a national laboratory which included over 190,000 patients from 50 states in America. They matched positive results for Sars-cov-2 with Vitamin D status where it was taken within the previous 12 months. The positivity rates among 3 Vitamin D range levels were as follows, 12.5% if "deficient" (<20 ng/ml or <50 nmol/L), 8.1% if "adequate" (30 - 34 ng/ml

(75 - 85 nmol/L), and 5.9% if the level was above 55 ng/ml (137.5 nmol/L) [23].

This risk of deficiency and therefore the potential benefit of supplementation were highlighted once more in an Iranian study of 235 patients whereby Vitamin D was measured on admission. They discovered that 74% developed severe Covid-19 infection (as per CDC criteria), and 32.8% had Vitamin D deficiency. The mortality rates of patients over 40 with and without sufficient Vitamin D were 9.7% and 20% respectively [24]. There was also a significant association between Vitamin D sufficiency and reduced clinical severity, levels of C-reactive protein (CRP) and increase in lymphocyte percentage. This suggests an important role on modulating the immune response in Covid.

Vitamin D deficiency is common, and levels decrease rapidly after admission to ICU [25] [26], a potential for intervention, where data suggests that Vitamin D is favourable in the prevention in the prevention of if viral infections or at least their severity, including Covid-19. This has great implications for reducing the burden of admission to hospital and ICU, particularly where resources are limited.

Governmental recommendations for vitamin D intake—400 IU/day for the UK and 600 IU/day for the USA (800 IU for >70 years) and the EU—are based primarily on bone health and may be woefully inadequate in the context of a viral pandemic. Recently published papers have proposed that more than 4000 IU per day of vitamin D3 may carry a risk of harm, citing the UK Scientific Advisory Committee on Nutrition (SACN) report of 2016 which set the recommended Upper Level (UL) intakes at 2000 IU (50 mcg) per day [27]. The report states: "Excessive vitamin D intakes have, however, been shown to have toxic effects (Vieth, 2006)".

However, this is misrepresentative as the Vieth paper states "Published reports suggest toxicity may occur with 25(OH)D concentrations beyond 500 nmol/L".

This in fact leaves a wide margin of safety as one would need to consume approximately 30,000 IU a day for three months to reach serum levels of 500 nmol/l to even run the risk of toxicity.

A systematic review and meta-analysis of individual participant data for the use of Vitamin D supplementation to prevent Respiratory tract infections, found that it did not influence risk of serious adverse events of any cause (adjusted odds ratio 0.98, 0.80 to 1.20; 11,224 participants in 25 studies) or death due to any cause (1.39, 0.85 to 2.27; 11,224 participants in 25 studies) [28].

Instances of potential adverse effects were rare; hypercalcaemia (0.6% vs 0.5% in control group) and renal stones (0.1% vs 0.2% in control group). When this analysis was stratified by dosing frequency it did not reveal any statistically significant increase in risk of adverse events with either bolus dosing or daily or weekly supplementation.

In another study evaluating the effects of various doses of chronic supplementation of Vitamin D, they found Serum 25(OH)D concentrations up to 300 nmol/L were achieved without disruption of calcium homeostasis or incidence

of toxicity. Hypercalcemia and hypercalciuria were not related to an increase in 25(OH)D concentrations nor vitamin D dose and Serum 25(OH)D concentrations up to 300 nmol/L were found to be safe [29].

Another report theorised that does of up to 10,000 IU/day is safe but likely above what is required and doses between 1000 - 2000 IU may be all that is required to produce optimal effects on immunity [30].

Vitamin D supplementation is recognised as a safe intervention.

Addressing Covid-19 specifically, one expert recommends in order to reduce risk of infection, people at risk should consume 10,000 IU/day of Vitamin D3 for a few weeks to quickly load and raise 25(OH)D concentrations. This should then be followed by 5000 IU/day, with the overall goal to achieve concentrations 100 - 150 nmol/L [31].

In order to achieve average serum 25(OH)D levels >100 nmol/L, the average required doses of Vitamin D related to BMI are as follows:

- 6000 IU/d for normal Body Mass Index (BMI);
- 7000 IU/d for overweight;
- 8000 IU/d for obese.

Doses of vitamin D in excess of 6000 IU/d were required to achieve serum 25(OH)D concentrations above 100 nmol/L [31].

In the critically ill, doses have varied significantly in what has been published in RCTs ranging from 200,000 - 600,000 IU given enterally usually in a single dose [16] [32] [33]. Based on the Castillo *et al*. trial, The MATH+ protocol [34] recommends a single large dose of cholecalciferol (if calcifediol is not available) of 300,000 IU (for body weight 69 - 90 kg). The levels should be rechecked on day 5. If serum levels <20 ng/ml, further supplemental doses of 96,000 IU/day for 5 days should be given.

As per the Front Line Covid-19 Critical Care Alliance (FLCCC):

"*The MATH+ protocol was created to treat patients in hospital and intensive care units, based on using therapies such as anti-inflammatory corticosteroids* (*Methylprednisolone*), *high-dose intravenous Vitamin C* (*Ascorbic acid*), *Vitamin B*1 (*Thiamine*), *and an anticoagulant* (*Heparin*), *plus co-interventions such as antivirals and supplements* (MATH+).

The core principle of MATH+ *is the use of anti-inflammatory agents to dampen the "cytokine storms," together with anticoagulation to limit the microvascular and macrovascular clotting, and supplemental oxygen to help overcome the hypoxia. Endothelial damage and an imbalance of both innate and adaptive immune responses, with aberrant macrophage activation, plays a central role in the pathogenesis of the severe* COVID-19 *disease. It is critically important to recognize that infection with* SARS-CoV-2, *the virus that causes* COVID-19, *progresses through stages. Treatment approaches are therefore highly stage-specific*".

2. Aim/Objectives

Initial, sporadic testing has revealed very high percentages of Vitamin D defi-

ciency although this is informal and not controlled.

We aim to assess levels of Vitamin D deficiency in ICU patients who have tested positive for Sars-Cov-2 and who have exhibited respiratory symptoms.

In this way, we hope to identify the possibility of Vitamin D as a significant contributing factor to disease progression in Covid patients. Specifically, we will measure:

1) How many Covid patients admitted to ICU had their Vitamin D status checked during their hospital admission and what delay there might have been in testing;

2) The Vitamin D status of these patients;

3) The time taken between being a positive PCR test and having Vitamin D checked and then treated;

4) How many patients that were deficient were treated and using what regime.

3. Standards/Guidelines/Protocols

In Dorset County Hospital (DCH) or the wider National Health Service, there exists no protocol for the testing and treatment of Vitamin D in patients with Covid.

As outlined in "Background" the MATH protocol stands as the most practical method of identifying and treating Vitamin D deficiency in the Covid patient. The full protocol can be found here:
https://covid19criticalcare.com/covid-19-protocols/math-plus-protocol/

4. Sample

Inclusion criteria:

- Male or Female;
- Patients of any age;
- Admitted to the Intensive Care Unit exhibiting respiratory symptoms, with a positive Sars-Cov-2 PCR test;
- Comorbidities not taken into account;
- Admitted between 12/3/21 and 25/2/21;
- Dorset County Hospital (single centre).

Sample size total: 79.

Audit type: Retrospective and Prospective ward-based Audit.

5. Methodology

Patients were identified through clerking to ICU. Patient information relating to biochemistry (such as vitamin D levels) and medical and drug history were obtained from electronic medical records available on ICE/JAC/DPR (Various digital records, Prescription and Results Software).

Vitamin D levels were measured using electrochemiluminescence immunoassay.

The data fields included are listed as below:

- Patient's hospital number;
- Date of birth;
- Age;
- Gender;
- Date of admission;
- Discharge date;
- Date of positive COVID19 PCR test;
- Date vitamin D levels were checked;
- Delay (in days) between positive PCR test and Vitamin D level check;
- Vitamin D level in nmol/L;
- Vitamin D dose given in units;
- Date vitamin D was given;
- Repeat date for Vitamin D level checking;
- Repeat Vitamin D level;
- Outcome (whether discharged from hospital or died);
- Duration of admission.

Once collected, the raw data was anonymised to protect patient confidentiality.

6. Key Findings

- Of the 79 Covid-19 Patients admitted to ICU, only 67.1% had their Vitamin D levels checked at any point during their hospital admission.
- The Average (Mode/Median) time between a patient having a positive PCR test and being tested for Vitamin D was 6.46/2 days.
- Of the 53 who had their Vitamin D status checked, 34 (64%) were determined to be deficient using 50 nmol/L as a cut-off. See below for a breakdown by age.

Figure 1 below shows the average level of vitamin D in patients according to

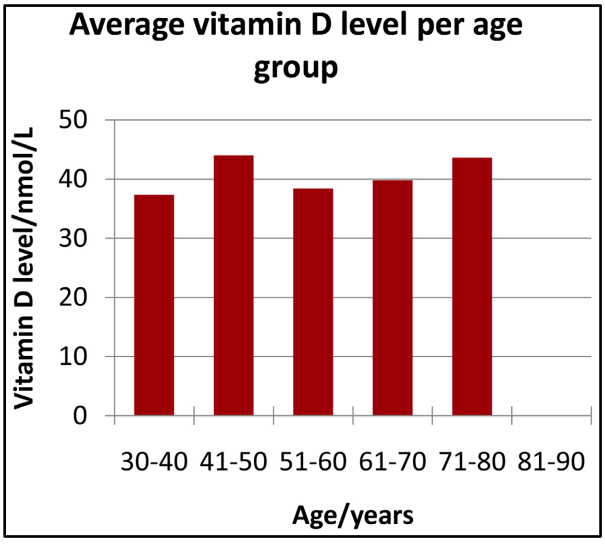

Figure 1. Average vitamin D level per age group.

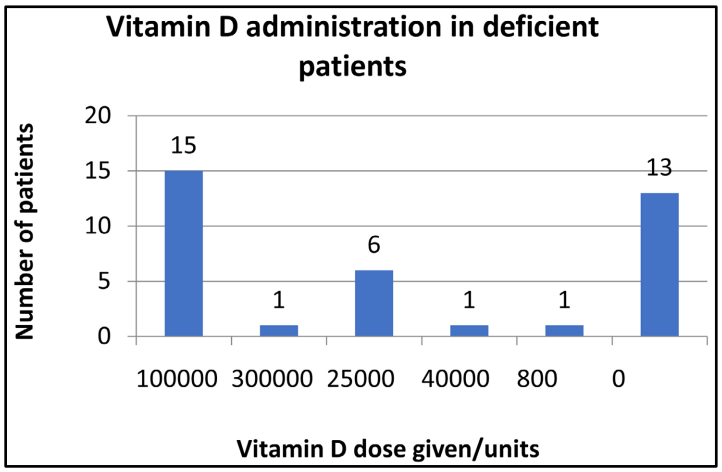

Figure 2. Vitamin D administration regimes in deficient patients.

the age group. Across all age groups, it can be clearly seen that for the group of patients studied, the average serum vitamin D level falls in the "deficient" category, assuming a cut off level of <50 nmol/L.

- The average delay between a positive Sars-cov-2 PCR test and receiving vitamin D supplementation was, on average (Mode/Median), 5.53/4 days.
- The treatment regime varied widely in terms of doses, frequency and timing. Range included 800 - 100,000 UI, with 100,000 being the most frequently administered, given as a single dose. In addition, little to know re-testing was performed of Vitamin D after dosing.

Figure 2 depicts the frequency of, and type of vitamin D regime administered to patients. 15 out of the 79 patients were given 100,000 units of vitamin D but 13 patients were not given any vitamin D supplementation despite being deficient. This chart also highlights the disparities in the vitamin D regimens prescribed.

7. Conclusions

1) Most patients admitted to ICU with Covid-19 are severely deficient in Vitamin D, despite many taking Vitamin D supplements as part of regular medications. When measuring against the optimal level of Vitamin D to protect against Covid-19, as stated in the evidence and recommendations outlined, as much as 100% of participants were deficient.

2) There currently exists disparity in the management of Covid-19 in terms of the use of Vitamin D; testing levels, delay in treatment and treatment regime with some patients not receiving any Vitamin replacement despite being deficient.

8. Discussion

This audit measured several important factors in patient care and in doing so produced some interesting conclusions. However, it represents a relatively small

fraction in the overall assessment of Vitamin D as a potential critical factor in the Covid-19 disease process.

What it does show, is a very strong correlation between Vitamin D deficiency and the severity of Covid-19, as hypothesised and in keeping with theoretical explanation and current research. To prove this link, it would be helpful to assess Vitamin D status in a local sample of healthy individuals and those with Covid-19 at all stages of the disease process for comparison. Thankfully, by exposing this Vitamin deficiency, it poses a positive sign for potentially improving patient care and outcome.

There is growing evidence that minimum 100 nmol/L of 25OH-D levels are needed to reduce the risk of Covid-19 but also cancers (e.g., colorectal), cardiovascular disease, infectious diseases, pathological pregnancies (e.g., preeclampsia, gestational diabetes, preterm birth), systemic connective tissue diseases and diabetes [31] [35]-[41]. In this study of ICU Covid-19 patients, 64% were shown to be deficient by normal hospital standards however, if we measure against the serum level outlined in the literature of 100 nmol/L, then every patient was deficient, supporting this claim. We must also recognise the rate of Vitamin D deficiency in the critically unwell is likely higher given the number of elderly who died or were at least gravely unwell, who were not admitted to ICU. Despite our growing understanding of its prophylactic capabilities in several diseases it remains disregarded in treatment protocols and disease guidance. Its relevance is enriched when we consider the global prevalence of Vitamin D deficiency (between 14% - 59%) [42], with potential for higher rates as populations move towards more industrialised living with less natural light exposure.

Such a shortfall in assessment and treatment of low Vitamin D Levels necessitates a more structured approach, especially when considering a pandemic response.

We must however also consider confounding elements that might explain such a correlation in the case of Covid-19. The most glaring is that those who are Vitamin D deficient may be more likely to have healthy diets and more active, outdoor lifestyles that would improve overall health and therefore immune response to Covid. Additionally, it may be that the disease process itself causes a rapid decline in Vitamin D and certain genetic or metabolic factors, independent of initial Vitamin D levels, may be at play. This too could also be explored by the recommendation above, assessing Covid at various disease stages and in a larger sample.

When evaluating this study and others mentioned, we must also contemplate the possibility of chronic diseases (Coeliac, liver disease, kidney disease) or use of certain drugs that could impair Vitamin D metabolism. Similarly, we may consider other nutritional deficiencies. Magnesium acts as a cofactor in many enzymes involved in Vitamin D metabolism. Moreover, chronic low calcium intake aggravate low Vitamin D status due to compensatory hyperparathyroidism that increases the production of calcitriol in the kidney from 25OH-D, and

this consequently contributes to diminishing serum 25OH-D levels. These should therefore been measure and addressed when approaching optimal Vitamin D treatment.

Regarding various treatment methods across this study and others examined, one point to note is Vitamin D3 requires hydroxylation to become 25(OH)D, a process that largely takes place in the liver [43]. This may be a saturable process [44] which, along with baseline levels of 25(OH)D may explain variations in dose response [45]. This should be accounted for. When given in an ICU setting where mortality rate is high in the Covid population, any delay may be enough to nullify any potential benefit. What's more, in this study, no consideration of body weight or comorbidities was considered when deciding on dosing.

An alternative, Calcifediol is already 25-hydroxylated, and thus, it bypasses the liver and becomes available in the circulation within four hours of administration.

What we also showed is limited testing of this crucial hormone. There appears very little uniformity in doing so with an inexcusable delay in testing, with many patients going without having levels tested at all. Given this is an easily identified and corrected deficiency that could have a key role in disease progression, this should be prioritised.

Certain delays in both evaluation and treatment of Vitamin D deficiency for some patients can be explained by the positive PCR being obtained in the community and therefore unknown to hospital/ICU staff until admission. This creates an unfair assessment of the delay in treatment for hospital staff but does not excuse the primary care's role in early treatment and prevention.

Most Covid-19 patients become most unwell at approximately 10-days from infection. Those who undergo a severe immune reaction in the form of a cytokine storm are most likely to require ICU admission. By this point it is the body's auto-immune reaction that poses greatest potential threat to life. Whilst Vitamin D has roles in both modulating auto-immune response and reducing likelihood and severity of viral illnesses, it is quite possible that intervention at this stage is of limited value given the excessive inflammation. The research indicates a strong link between Vitamin D and prophylaxis. ICU wards nationally have been under stress due to admissions during the pandemic whilst hospital beds in general have been well below capacity.

We have the benefit of a wide surveillance and early diagnosis scheme with free testing for anyone of the public with any symptoms or positive contact history, long before admission. For these reasons, early intervention or at least, assessment for early intervention using Vitamin D seems paramount as a way of reducing ICU burden.

What the results also illustrated was huge variance in the dose of Cholecalciferol given, with no further testing done to assess the adequacy of the choice of dose. This seems an unfortunate oversight. As a novel disease with a limited arsenal of evidence-based hospital treatments allowed by the NHS, here is an easily

corrected, immunodeficiency that is widespread in Covid patients. Given Vitamin D is both inexpensive with a very limited side effect profile, it seems prudent that whilst more research is done on Vitamin D and on other treatments, that a more uniform approach be taken in correcting simple immune deficiencies.

The results of this audit do present a potential shortfall in care that, if addressed could theoretically reduce ICU admission, length of stay and even, mortality. Whilst it did not measure outcomes it has laid the groundwork for doing so. These initial findings are significant enough to warrant further research in this area.

Expanding on the global research undertaken already, this audit aimed to assess the potential implication of Vitamin D in the Covid-19 disease process localised to DCH. In doing so it stands as a foothold to expand into further areas of research, analysing outcomes of different treatment regimes, measuring ICU admission, length of stay, mortality, assessing timing of intervention including community roles and the potential for early intervention in avoiding hospital admission altogether.

9. Limitations/Considerations

- No guidelines at DCH exist that relate to this topic directly and therefore treatment is decided between various teams based on experience and clinical knowledge therefore, it cannot be expected there would be consistency in response. This inconsistency is enhanced by the novel nature of this disease with research ongoing.
- In theory, given high pressures for ITU beds in this period, many elderly Covid patients with Covid were not admitted to ITU, due to a limited treatment escalation plan. This would explain the relatively young study sample despite Covid affecting the elderly most severely, more commonly. This may skew the results significantly, where an even greater correlation between Vitamin D and clinical severity/mortality could be expected. Assessment earlier in the disease process would help in validating this.
- We must also consider our presence on the ICU ward during this period whereby our interest in Vitamin D may have influenced and encouraged the decisions to test and treat Vitamin D. ICU staff were aware to some degree of the ongoing research but were not given any instruction as to treatment and we did not impose any suggestion as to when to test for Vitamin D in our absence.
- A larger more varied sample would benefit the study. This study was limited by its sample size of 79, given the timeframe for data collection and the relatively small ICU unit in which it occurred. As with any small sample size, data may be misrepresentative of the larger population and thus false conclusions drawn. The sample was also limited to local population with little racial variance which is skewed to an older Caucasian population with high rates of comorbidity

and smoking.

- A great thank you to the tireless ICU team during this pandemic who supported us in our work, and the amazing patients we had the privilege of treating.

10. Further Research

As alluded to above, this has paved the way for several further explorations into the potentially life-saving role of Vitamin D. It would be recommended that the following are considered:

- Testing Vitamin D status at admission to hospital or in the community.
- Measuring outcomes based on Vitamin D status.
- Measuring outcomes based on Vitamin D treatments.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Dusso, A.S., Brown, A.J. and Slatopolsky, E. (2005) Vitamin D. *American Journal of Physiology-Renal Physiology*, **289**, F8-F28. https://doi.org/10.1152/ajprenal.00336.2004

[2] Rondanelli, M., Miccono, A., Lamburghini, S., *et al*. (2018) Self-Care for Common Colds: The Pivotal Role of Vitamin D, Vitamin C, Zinc, and *Echinacea* in Three Main Immune Interactive Clusters (Physical Barriers, Innate and Adaptive Immunity) Involved during an Episode of Common Colds—Practical Advice on Dosages and on the Time to Take These Nutrients/Botanicals in order to Prevent or Treat Common Colds. *Evidence-Based Complementary and Alternative Medicine*, **2018**, Article ID: 583095. https://doi.org/10.1155/2018/5813095

[3] Aranow, C. (2011) Vitamin D and the Immune System. *Journal of Investigative Medicine*, **59**, 881-886. https://doi.org/10.2310/JIM.0b013e31821b8755

[4] Hughes, D.A. and Norton, R. (2009) Vitamin D and Respiratory Health. *Clinical and Experimental Immunology*, **158**, 20-25. https://doi.org/10.1111/j.1365-2249.2009.04001.x

[5] Martineau, A.R., *et al*. (2017) Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data. *BMJ*, **356**, Article No. i6583.

[6] Huang, C., Wang, Y., Li, X., *et al*. (2020) Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet*, **395**, 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[7] Sharifi, A., Vahedi, H., Nedjat, S., Rafiei, H. and Hosseinzadeh-Attar, M.J. (2019) Effect of Single-Dose Injection of Vitamin D on Immune Cytokines in Ulcerative Colitis Patients: A Randomized Placebo-Controlled Trial. *APMIS*, **127**, 681-687. https://doi.org/10.1111/apm.12982

[8] Rossi, G.A., Fanous, H. and Colin, A.A. (2020) Viral Strategies Predisposing to Respiratory Bacterial Superinfections. *Pediatric Pulmonology*, **55**, 1061-1073. https://doi.org/10.1002/ppul.24699

[9] Ajabshir, S., Asif, A. and Nayer, A. (2014) The Effects of Vitamin D on the Renin-

Angiotensin System. *Journal of Nephropathology*, **3**, 41-43.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999581/

[10] Dijkman, R., Jebbink, F., Deijs, M., Milewska, A., Pyrc, K., *et al*. (2012). Replication-Dependent Downregulation of Cellular Angiotensin-Converting Enzyme 2 Protein Expression by Human Coronavirus NL63. *Journal of General Virology*, **93**, 1924-1929. https://doi.org/10.1099/vir.0.043919-0

[11] Ilie, P.C., Stefanescu, S. and Smith, L. (2020) The Role of Vitamin D in the Prevention of Coronavirus Disease 2019 Infection and Mortality. *Aging Clinical and Experimental Research*, **32**, 1195-1198
https://link.springer.com/content/pdf/10.1007/s40520-020-01570-8.pdf
https://doi.org/10.1007/s40520-020-01570-8

[12] Rhodes, J.M., Subramanian, S., Laird, E. and Kenny, R.A. (2020) Letter: Low Population Mortality from COVID-19 in Countries South of Latitude 35° North Supports Vitamin D as a Factor Determining Severity. Authors' Reply. *Alimentary Pharmacology & Therapeutics*, **52**, 412-413. https://doi.org/10.1111/apt.15823

[13] Cannell, J.J., Vieth, R., Umhau, J.C., *et al*. (2006) Epidemic Influenza and Vitamin D. *Epidemiology & Infection*, **134**, 1129-1140.
https://doi.org/10.1017/S0950268806007175

[14] Patel, J.V., Chackathayil, J., Hughes, E.A., Webster, C., Lip, G.Y. and Gill, P.S. (2013) Vitamin D Deficiency amongst Minority Ethnic Groups in the UK: A Cross Sectional Study. *International Journal of Cardiology*, **167**, 2172-2176.
https://doi.org/10.1016/j.ijcard.2012.05.081

[15] Khunti, K., Singh, A.K., Pareek, M. and Hanif, W. (2020) Is Ethnicity Linked to Incidence or Outcomes of COVID-19? *BMJ*, **369**, Article No. m1548.
https://doi.org/10.1136/bmj.m1548

[16] Putzu, A., Belletti, A., Cassina, T., *et al*. (2017) Vitamin D and Outcomes in Adult Critically Ill Patients. A Systematic Review and Meta-Analysis of Randomized Trials. *Journal of Critical Care*, **38**, 109-114.
https://doi.org/10.1016/j.jcrc.2016.10.029

[17] Ginde, A.A., Brower, R.G., Caterino, J.M., *et al*. (2019) Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D-Deficient Patients. *New England Journal of Medicine*, **381**, 2529-2540. https://doi.org/10.1056/NEJMoa1911124

[18] Zhang, Y., Leung, D.Y. and Goleva, E. (2014) Anti-Inflammatory and Corticosteroid-Enhancing Actions of Vitamin D in Monocytes of Patients with Steroid-Resistant and Those with Steroid-Sensitive Asthma. *Journal of Allergy and Clinical Immunology*, **133**, 1744-1752. https://doi.org/10.1016/j.jaci.2013.12.004

[19] Mahboub, B., Al Heialy, S., Hachim, M.Y., Ramakrishnan, R.K., Alzaabi, A., Seliem, R.M., Salameh, L.I., Toor, S.M., Shendi, F.S., Al Ali, O.M., Safarini, B.K., Erabia, W.T., Halwani, R. and Hamid, Q. (2021) Vitamin D Regulates the Expression of Glucocorticoid Receptors in Blood of Severe Asthmatic Patients. *Journal of Immunology Research*, **2021**, Article ID: 9947370.
https://doi.org/10.1155/2021/9947370

[20] Ehrchen, J.M., Roth, J. and Barczyk-Kahlert, K. (2019) More than Suppression: Glucocorticoid Action on Monocytes and Macrophages. *Frontiers in Immunology*, **10**, Article 2028. https://doi.org/10.3389/fimmu.2019.02028

[21] Calton, E.K., Keane, K.N., Newsholme, P. and Soares, M.J. (2015) The Impact of Vitamin D Levels on Inflammatory Status: A Systematic Review of Immune Cell Studies. *PLOS ONE*, **10**, e0141770. https://doi.org/10.1371/journal.pone.0141770

[22] Castillo, M.E., Entrenas Costa, L.M., Vaquero Barrios, J.M., *et al*. (2020) Effect of

Calcifediol Treatment and Best Available Therapy versus Best Available Therapy on Intensive Care Unit Admission and Mortality among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical Study. *The Journal of Steroid Biochemistry and Molecular Biology*, **203**, Article ID: 105751. https://doi.org/10.1016/j.jsbmb.2020.105751

[23] Kaufman, H.W., Niles, J.K., Kroll, M.H., Bi, C. and Holick, M.F. (2020) SARS-CoV-2 Positivity Rates Associated with Circulating 25-Hydroxyvitamin D Levels. *PLOS ONE*, **15**, e0239252. https://doi.org/10.1371/journal.pone.0239252

[24] Maghbooli, Z., Sahraian, M.A., Ebrahimi, M., Pazoki, M., Kafan, S., Tabriz, H.M., *et al*. (2020) Vitamin D Sufficiency, a Serum 25-Hydroxyvitamin D at Least 30 ng/mL Reduced Risk for Adverse Clinical Outcomes in Patients with COVID-19 Infection. *PLOS ONE*, **15**, e0239799. https://doi.org/10.1371/journal.pone.0239799

[25] Venkatesh, B. and Nair, P. (2014) Hypovitaminosis D and Morbidity in Critical Illness: Is There Proof beyond Reasonable Doubt? *Critical Care*, **18**, Article No. 138. https://doi.org/10.1186/cc13863

[26] Lee, P., Eisman, J.A. and Center, J.R. (2009) Vitamin D Deficiency in Critically Ill Patients. *New England Journal of Medicine*, **350**, 1912-1914. https://doi.org/10.1056/NEJMc0809996

[27] UK Scientific Advisory Committee on Nutrition (SACN) (2016) Vitamin D and Health. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf

[28] Martineau, A.R., Jolliffe, D.A., Hooper, R.L., *et al*. (2017) Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data. *BMJ*, **356**, Article No. i6583. https://doi.org/10.1136/bmj.i6583

[29] Kimball, S.M., Mirhosseini, N. and Holick, M.F. (2017) Evaluation of Vitamin D_3 Intakes Up to 15,000 International Units/Day and Serum 25-Hydroxyvitamin D Concentrations Up to 300 nmol/L on Calcium Metabolism in a Community Setting. *Dermato-Endocrinology*, **9**, e1300213. https://doi.org/10.1080/19381980.2017.1300213

[30] Bergman, P. (2020) The Link between Vitamin D and Covid-19: Distinguishing Facts from Fiction. *Journal of Internal Medicine*, **289**, 131-133. https://doi.org/10.1111/joim.13158

[31] Grant, W.B., Lahore, H., McDonnell, S.L., Baggerly, C.A., French, C.B., Aliano, J.L. and Bhattoa, H.P. (2020) Evidence That Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, **12**, Article No. 988. https://doi.org/10.3390/nu12040988

[32] Han, J.E., Jones, J.L., Tangpricha, V., *et al*. (2016) High Dose Vitamin D Administration in Ventilated Intensive Care Unit Patients: A Pilot Double Blind Randomized Controlled Trial. *Journal of Clinical & Translational Endocrinology*, **4**, 59-65. https://doi.org/10.1016/j.jcte.2016.04.004

[33] Amrein, K., Schnedl, C., Berghold, A., *et al*. (2014) Correction of Vitamin D Deficiency in Critically Ill Patients: A Randomized Placebo-Controlled Trial. *Clinical Nutrition*, **33**, S13. https://doi.org/10.1016/S0261-5614(14)50030-1

[34] Kory, P., Meduri, G.U., Iglesias, J., Varon, J., Cadegiani, F.A. and Marik, P.E. (2022) "MATH+" Multi-Modal Hospital Treatment Protocol for COVID-19 Infection: Clinical and Scientific Rationale. *Journal of Clinical Medicine Research*, **14**, 53-79. https://doi.org/10.14740/jocmr4658

[35] Yisak, H., Ewunetei, A., Kefale, B., Mamuye, M., Teshome, F., Ambaw, B. and Yideg

Yitbarek, G. (2021) Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review. *Risk Management and Healthcare Policy*, **14**, 31-38. https://doi.org/10.2147/RMHP.S291584

[36] Pludowski, P., Holick, M.F., Grant, W.B., Konstantynowicz, J., Mascarenhas, M.R., Haq, A., Povoroznyuk, V., Balatska, N., Barbosa, A.P., Karonova, T., *et al*. (2018) Vitamin D Supplementation Guidelines. *The Journal of Steroid Biochemistry and Molecular Biology*, **175**, 125-135. https://doi.org/10.1016/j.jsbmb.2017.01.021

[37] Kimball, S.M. and Holick, M.F. (2020) Official Recommendations for Vitamin D through the Life Stages in Developed Countries. *European Journal of Clinical Nutrition*, **74**, 1514-1518. https://doi.org/10.1038/s41430-020-00706-3

[38] Ebadi, M. and Montano-Loza, A.J. (2020) Perspective: Improving Vitamin D Status in the Management of COVID-19. *European Journal of Clinical Nutrition*, **74**, 856-859. https://doi.org/10.1038/s41430-020-0661-0

[39] Wimalawansa, S.J. (2020) Global Epidemic of Coronavirus—COVID-19: What Can We Do to Minimize Risks. *European Journal of Biomedical and Pharmaceutical Sciences*, **7**, 432-438.

[40] Charoenngam, N. and Holick, M.F. (2020) Immunologic Effects of Vitamin D on Human Health and Disease. *Nutrients*, **12**, Article No. 2097. https://doi.org/10.3390/nu12072097

[41] Charoenngam, N., Shirvani, A. and Holick, M.F. (2021) Vitamin D and Its Potential Benefit for the COVID-19 Pandemic. *Endocrine Practice*, **27**, 484-493. https://doi.org/10.1016/j.eprac.2021.03.006

[42] Hovsepian, S., Amini, M., Aminorroaya, A., Amini, P. and Iraj, B. (2011) Prevalence of Vitamin D Deficiency among Adult Population of Isfahan City, Iran. *Journal of Health, Population and Nutrition*, **29**, 149-155. https://doi.org/10.3329/jhpn.v29i2.7857

[43] Daniel, D. and Bikle, D.D. (2021) Vitamin D: Production, Metabolism and Mechanisms of Action. In: Feingold, K.R., Anawalt, B., Blackman, M.R., *et al*., Eds., *Endotext*, MDText.com, Inc., South Dartmouth (MA). https://www.ncbi.nlm.nih.gov/books/NBK278935/#

[44] Ramasamy, I. (2020) Vitamin D Metabolism and Guidelines for Vitamin D Supplementation. *The Clinical Biochemist Reviews*, **41**, 103-126.

[45] Trang, H.M., Cole, D.E., Rubin, L.A., Pierratos, A., Siu, S. and Vieth, R. (1998) Evidence that Vitamin D_3 Increases Serum 25-Hydroxyvitamin D More Efficiently Than Does Vitamin D_2. *The American Journal of Clinical Nutrition*, **68**, 854-858. https://doi.org/10.1093/ajcn/68.4.854