

# Mild COVID-19 manifestation in multiple risk factor patient on methotrexate, who had been treated with UVB phototherapy and had sufficient plasma 25-OH-vitamin D3 level

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## Abstract

We report mild COVID-19 manifestation in high-risk patient with sufficient plasma 25-OH-Vitamin D3 level. Given the global pandemic of vitamin D deficiency, as well as its likely beneficial effects during SARS-CoV-2 infection, report highlights importance of routine 25-OH-Vitamin D3 measurement, either for clinical course prediction or deciding on supplementation.

## Introduction

During the recent COVID-19 pandemic, several well defined conditions have been recognized as a risk factors worsening disease course and outcome.<sup>1,2</sup> The most important risk factors which can lead to severe COVID-19 symptomatology are obesity, diabetes mellitus, hypertension, age over 65 years and immunosuppressive therapy.<sup>3,4</sup> These conditions are thought to affect host responses to infection by various mechanisms, enhancing and accelerating the harmful pathophysiological processes.<sup>5</sup> The COVID-19 pathogenesis upon SARS-CoV-2 infection is characterized by initial viral evasion from targeted immune response, followed by excessive and undirected immune activation causing subsequent hyper inflammatory response<sup>6</sup>. Patients with risk factors more likely react with extremely excessive systemic inflammation resulting with cytokine storm which is considered as an executive pathophysiological mechanism responsible for severe disease manifestations, such as acute respiratory distress syndrome (ARDS), diffuse endothelial damage with accelerated thrombogenesis and multiple organ dysfunction syndrome (MODS)<sup>6</sup>. In most groups of risk patients, common mechanism favoring development of excessive inflammation and cytokine storm is persistently present proinflammatory milieu<sup>7</sup>. Such chronic proinflammatory state can arises either due to hypersecretion of proinflammatory adipokines in obese patients<sup>7</sup>, lack of anti-inflammatory signaling in diabetic and insulin-resistant patients<sup>7,8</sup> or dysregulation of renin angiotensin system (RAS) with increased proinflammatory angiotensin II (Ang II) production in hypertensive patients<sup>6,9,10</sup>. Patients on immunosuppressive therapy are considered to be at risk due to the facilitated viral multiplication and dissemination during the initial phase, enabling in turn more vigorous ignition of hyperinflammatory phase<sup>6,10,11</sup>. In the other hand, hyperactive inflammatory processes could be, in some extent, kept under control by immunosuppressants<sup>12</sup>, but conclusions and recommendations on their use in COVID-19 patients are inconsistent and unclear. Moreover, most intriguing obscurity during COVID-19 pandemic - enormous variability of clinical presentation and unpredictability of outcome, either in previously healthy or in at-risk patients, still remains enigmatic.

In effort to prevent adverse outcomes of SARS-CoV-2 infection, growing attention is paid to potentially protective factors alleviating disease severity, among which vitamin D3 is currently being in the spotlight. Namely, many "pre-corona" studies have found antiviral, immunomodulatory, and anti-inflammatory properties of vitamin D3<sup>13</sup>, suggesting this data could be extrapolated to SARS-CoV-2 infection<sup>14,15</sup>. Assumptions

on beneficial effects of vitamin D3 in COVID-19 patients have recently been verified by several convincing clinical and interventional studies<sup>16-24</sup>. The importance of this topic is highlighted by data showing that the global pandemic of hypovitaminosis Dis being ongoing concomitantly with the COVID-19 pandemic<sup>25-28</sup>.

Here, we report mild clinical COVID-19 presentation in high-risk patient with the satisfactory vitamin D3 level upon UVB phototherapy treatment, pointing to the vitamin D3 as a likely positive modulator of disease course, as well as to potential value of routine 25-OH-Vitamin D3 measurement in COVID-19 patients.

## Case report

66-years old Caucasian male sought medical advice due to slightly elevated body temperature (up to 37.50C), nausea without vomiting and occasional, mild, and dry cough during the last 2 days. He did not complain of dyspnea, shortness of breath, myalgias or arthralgias during that period. He did not notice any loss of sense of smell or taste. He denied recent traveling or contacts with symptomatic persons. On admission patient was alert, conscious, oriented, and independently movable and he was seeming to be in good general condition. Physical examination revealed pulse rate of 100 bpm, respiratory rate of 16 bpm, arterial blood pressure of 147/75 mm Hg and axillary measured body temperature of 37.50C. Chest auscultation disclosed clear breath sounds without obvious moist/dry rales or crackles, as well as normal heart sounds without audible murmurs. Abdomen was soft and painless on palpation, and no discomfort was elicited. Neither organomegaly nor palpable pathological masses were detected. The patient was obese, with a body weight of 99.5 kg and body height of 167 cm, resulting in a body mass index (BMI) of 35.7. He had been passionate smoker for a long period of time, and he stopped smoking 6 years ago. Before 25 years, patient has been diagnosed with psoriasis. Severe psoriatic arthritis has occurred 6 years ago, and since that time he has been continuously receiving methotrexate at the dose of 15 mg/week subcutaneously. Folic acid in the dose of 5 mg twice weekly was prescribed to prevent folate deficiency. Three months before the actual presentation cutaneous psoriatic symptomatology exacerbated, and the patient was undergoing to UVB narrow band phototherapy lasting for two months.

Patient was diagnosed with arterial hypertension 8 years ago, and diagnosis of type 2 diabetes mellitus (T2DM) has been established 6 years ago. To treat these conditions, he has been regularly taking losartan with hydrochlorothiazide (50 mg+12.5 mg once a day) and metformin (500 mg three times a day).

The patient was referred to COVID-19 testing, and nasopharyngeal swab was taken. Detection of viral RNA by GeneXpert SARS-CoV-2 RT-PCR assay (Cepheid) resulted in a positive finding. A chest X-ray was done and finding was unremarkable, without any opacity indicating infiltration or consolidation. Blood oxygen saturation (SpO2) measured by pulse oximeter was 95%. Subsequent routine laboratory tests found slightly elevated C-reactive protein (7 mg/L); increased erythrocyte sedimentation rate (50 mm/hr); normal white blood cell count ( $4.8 \times 10^9/L$ ) with lymphopenia ( $1.02 \times 10^9/L$ ); decreased red blood cell count ( $4.06 \times 10^{12}/L$ ), hematocrit (0.387) and hemoglobin concentration (132 g/L); hyperglycemia (10.1 mmol/L), hypercreatininemia (134  $\mu L/L$ ) and hypertriglyceridemia (1.8 mmol/L). Semi quantitative dipstick urinalysis indicated mild proteinuria (1+). Further laboratory investigations revealed normal plasma 25-OH-vitamin D3 concentration of 92.2 nmol/L (normal range 50.0 – 125.0 nmol/L). All laboratory parameters, alongside with corresponding normal ranges, are shown in the Table 1.

Considering the mild clinical picture, no therapy was introduced, and all previous medications were continued. Given the occupancy of hospital facilities with severe cases, the patient was monitored on an outpatient basis. His condition did not worse and presenting symptoms completely subsided within 3 days. Twenty days after the initial presentation SARS-CoV-2 RT-PCR test was negative, and serological enzyme-linked fluorescence assay (ELFA) showed presence of SARS-CoV-2 IgG (33.16) and IgM (5.09) in the patient's serum. During the next month, the patient felt well, not complaining of fatigue or exhaustion, and dermatological, rheumatological and internistic symptoms remained stationary.

## Discussion

Almost immediately after the pandemic outbreak in China, greater vulnerability and higher incidence of

severe clinical presentation and fatal outcome were observed in patients with particular preexisting conditions, especially in persons aged  $> 65^{1,2}$ . Numerous studies have shown that the greatest risk of severe COVID-19 course/manifestation is posed by the presence of either diabetes mellitus, obesity, arterial hypertension or immunosuppression / immunodeficiency<sup>3-8</sup>. Severe COVID-19 manifestations include development of extensive bilateral pneumonia, ARDS and endothelial damage accompanied with accelerated thrombogenesis, which can all lead to the respiratory and multiorgan failure, being major clinical concern due to intensive care units overcrowding and high mortality rate<sup>4,6</sup>.

According to the current knowledge, the basic pathogenetic mechanisms responsible for the propensity to severe COVID-19 course in the patients at risk could be reduced to a common denominator relating to facilitation and reinforcement of inflammatory processes. Inappropriately excessive and uncontrolled inflammation more likely can result with the development of autodestructive cytokine storm, which is considered to be the final effector mechanism of tissue damage<sup>4,6,10,11</sup>. Obesity, insulin resistance and diabetes mellitus, as well as hypertension, are characterized by the presence of persistent low-intensity inflammation, which may be decisive underlying factor amplifying and perpetuating viral-induced inflammatory response<sup>4-11</sup>. Some authors also suggest pathogenetic involvement of immunogenic damage-associated molecular patterns (DAMPs), released as a consequence of preexisting disease<sup>29</sup>. Immunosuppression is thought to favor more severe disease development by permitting faster viral replication resulting in extensive direct viral-mediated tissue damage<sup>4,6,11</sup>. In the other hand, immunosuppression can mitigate excessive inflammation. There are studies showing no increased risk of severe COVID-19 manifestation in patients on immunosuppressive therapy, including methotrexate<sup>30,31</sup>, as well as reports that emphasize severe COVID-19 course in such patients<sup>32,33</sup>. Accordingly, available data on the impact of variety of immunosuppressant therapy regarding COVID-19 clinical course are inconclusive yet<sup>30,34</sup>. Both, insufficient directed immune response as well as unpurposeful inflammatory overactivity are assumed to increase possibility of severe COVID-19 manifestations in the elderly patients, as aging is known to impair considerably the efficacy of immunoregulatory mechanisms<sup>35,36</sup>. The probability of severe COVID-19 increases with age and number of preexisting pathological conditions and is particularly high in patients with older age and more risk comorbidities<sup>37</sup>, indicating a cumulative effect of the risk factors.

Here we described a mild COVID-19 course, without any concerning symptoms or clinical signs, and with a favorable outcome in the patient with multiple conditions considered as risk factors: obesity, T2DM, hypertension, age  $> 65$  and immunosuppressive therapy. Laboratory findings of the proteinuria and hypercreatininemia also suggest renal function impairment, probably due to diabetic nephropathy development. Chronic renal failure was also found to be independently associated with poor clinical outcome<sup>38</sup>. Besides, given the long-standing history of psoriasis in our patient (25 years), we also point out that several studies have found increased risk of serious infection (especially cutaneous and respiratory) in psoriatic patients independently on the therapy and other comorbidities<sup>30,39,40</sup>. The risk of serious infection in psoriatic patients was found to increase further with the severity of the disease<sup>39</sup> and the presence of either diabetes mellitus, obesity, age  $> 60$  years<sup>41,42</sup> or history of smoking<sup>42</sup>. Taking into account the recent cutaneous exacerbation (three months before the actual presentation; treated by UVB phototherapy), our patient had all of the above conditions that may additionally increase the risk of severe infection in the context of psoriasis *per se*.

Laboratory findings in our patients, showing normal leukocyte count and only slightly elevated inflammatory markers, are in line with a mild clinical picture. The exception is lymphopenia, which has been found to be associated with severe COVID-19 cases<sup>37,38</sup>, but in presented patient lymphopenia very likely may be a consequence of long-term treatment with methotrexate, which is known to inhibit DNA synthesis and cause bone marrow toxicity<sup>43,44</sup>. Such causality can also be attributed to the anemia, found in our patient. Although there is a paucity of data on clear relationship between anemia and COVID-19 severity, one meta-analysis found an association of anemia with severe manifestation of COVID19, but not with mortality rate<sup>45</sup>.

We would like to emphasize the sufficient plasma 25-OH-vitamin D3 (calcifediol, precursor of an active form

of the vitamin D3) level in the presented patient, which could have had, at least in part, positive impact on the disease course and outcome. Namely, since time when the possible favorable effects of vitamin D3 in COVID-19 patients have been proposed<sup>14,15</sup>, several well designed and convincing studies have clearly shown association between vitamin D deficiency and more severe COVID-19 clinical manifestations<sup>16-20,46</sup>. Recent interventional studies provide further evidence on beneficial and protective impact of vitamin D3 among COVID-19 patients<sup>21-24</sup>. Protective vitamin D3 mechanisms in COVID-19 patients are presumed to be multiple, including potent immunomodulatory activity, antiviral peptide induction, enhancement of physical barrier integrity and even direct interference with viral replication<sup>13-15,47</sup>. Vitamin D-mediated suppression of excessive T helper cell type 1 (Th1) response and proinflammatory cytokine hypersecretion is considered as one of the most important effect that reduces the likelihood of cytokine storm development, major pathogenic event concerning severe COVID-19 manifestation<sup>14,15,47-49</sup>. Promoting induction of the T regulatory cells (Tregs), vitamin D may further enhance these immunomodulatory and anti-inflammatory effects<sup>15</sup>. Ability of vitamin D3 to induce production of type I interferons (IFNs) is also of great importance during SARS-CoV-2 infection, since type I IFNs has been known as the most powerful natural mediators of antiviral activity in humans, keeping viral replication under control and enabling effective viral clearance without excessive inflammatory response<sup>50</sup>. In addition, impaired or delayed type I IFNs response during early stage of SARS-CoV-2 infection have been found to play a major role in the cytokine storm development<sup>51,52</sup>, probably by allowing accelerated viral replication, which at a later stage leads to excessive inflammation.

Considering the available data on the protective vitamin D3 effects, but also the "pandemic" of vitamin D deficiency<sup>25-28</sup>, we can assume that in our patient, burdened by multiple risk factors, sufficient plasma 25-OH-vitamin D3 curbed detrimental immunopathogenic mechanisms and enabled favorable outcome. Since there are high prevalence of vitamin D3 deficiency in general population, with even more frequent occurrence among patients with obesity, T2DM and hypertension<sup>27,28</sup>, and our patient had not been supplemented *per os*, we can presume that sufficient level of 25-OH-vitamin D3 had been achieved by UVB phototherapy. This assumption complies to observed seasonal changes in COVID-19 symptom severity and incidence, which are the lesser during the periods with the longer sunlight duration<sup>15,53</sup>. However, such scenario with a complex pathophysiological constellation do not allow us to rule out the possible impact of the methotrexate therapy, as well as the influence of patient's genetic makeup on the course and outcome of the disease. It is also noteworthy that patient gained appropriate antiviral immunoglobulin levels, despite prolonged methotrexate treatment, since it is known that methotrexate can suppress the production of antibodies to neoantigens<sup>54-56</sup>. As vitamin D3 has been found to promote T helper type 2 (Th2) response, IL-4 production and Tregs generation<sup>15,57</sup>, such humoral outcome could also be supported by sufficient 25-OH-vitamin D3 status in described patient. Interestingly, an increase in the frequency of naïve B cells and Tregs after narrowband UVB phototherapy was previously shown<sup>58</sup>. These observations may be of great importance for improving COVID-19 vaccination efficacy, but further thorough studies are needed on this topic.

In conclusion, we point to likely possible role of vitamin D as a positive modifier of COVID-19 course and outcome and suggest that routine determination of 25-OH-vitamin D3 status could be considered as useful tool for, at least rough, estimation of COVID-19 outcome, as well as for deciding on vitamin D3 supplementation.

### Conflict of Interest

Both authors declare no conflicts of interest.

### Ethical Considerations

The patient was informed in detail and he provided written consent.

### Data Availability Statement

The data are not publicly available due to the protection of patient privacy and adherence to ethical principles. Clinical and laboratory data may be provided upon reasonable request to corresponding author.

### Author Contributions:

Martina Kralj managed the patient, collected the data, and contributed to the manuscript drafting.

Hrvoje Jakovac interpreted the findings, reviewed the literature, drafted, and wrote the manuscript.

Both authors have read and approved the final manuscript.

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Table 1. Laboratory findings upon detection of SARS-CoV-2 positivity (3 days after symptoms appeared = median time of symptoms duration)

Parameter (unit)	Result	Reference range
Total white blood cell ( $\times 10^9/\text{L}$ )	4.8	3.4– 9.7
Lymphocytes ( $\times 10^9/\text{L}$ )	1.02	1.19 – 3.35
Neutrophils ( $\times 10^9/\text{L}$ )	3.10	2.06 – 6.49
Monocytes ( $\times 10^9/\text{L}$ )	0.50	0.12 – 0.84
Eosinophils ( $\times 10^9/\text{L}$ )	0.15	0.00 – 0.43
Basophils ( $\times 10^9/\text{L}$ )	0.04	0.00 – 0.06
Red blood cell ( $\times 10^{12}/\text{L}$ )	4.06	4.34 – 5.72
Hematocrit (%)	0.387	0.415 – 0.530
Hemoglobin (g/L)	132	138 - 175
MCV (fL)	95.3	83.0 – 97.2
MCH (pg)	32.5	27.4 – 33.9
MCHC (g/L)	341	320 - 345
Platelets ( $\times 10^9/\text{L}$ )	240	158 - 424
MPV (fL)	9.7	6.8 – 10.4
Prothrombin time	0.96	> 0.7
C-reactive protein (mg/L)	7	0 - 5
Erythrocyte sedimentation rate – 1h (mm/3.6 ks)	50	3 - 23
Glucose (mmol/L)	10.1	4.4 – 6.4
Triglycerides (mmol/L)	1.8	< 1.7
Total cholesterol (mmol/L)	3.6	< 5.0
LDL cholesterol (mmol/L)	2.1	< 3.0
HDL cholesterol (mmol/L)	1.1	> 1.0
Urea (carbamide) (mmol/L)	7.5	2.8 – 8.3
Creatinine ( $\mu\text{mol/L}$ )	134	64 - 104
Total bilirubin ( $\mu\text{mol/L}$ )	10	3 - 20
25-OH-vitamin D3 (nmol/L)	92.2	50.0 – 125.0
Urinary proteins (dipstick)	1+	negative
Urinary glucose (dipstick)	negative	negative
SpO2 by pulse oximeter (%)	95	> 94