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VITAMIN D STATUS IN PATIENTS WITH COVID-19 - SEX DIFFERENCES ASSOCIATED WITH SEVERITY OF THE DISEASE.

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ABSTRACT

Background: Patients with COVID-19 can develop abnormal inflammatory response, which can progress to multiorgan failure and death, with a higher prevalence observed in men. Besides, recent research suggests a complex interaction between viral infections and vitamin D.

Aims: This study evaluates sex differences of vitamin D status, circulating enzymes and biomarkers of inflammatory response at the time of diagnosis of COVID-19, depending on severity of disease the patients develop.

Methods: This retrospective observational study was conducted from September to December 2020. Patients (n = 115) were divided in two groups: Group A- asymptomatic or mild cases (36 men and 19 women; mean age 53.3 ± 1.4 y.) and Group B- patients who develop moderate or severe COVID-19 requiring hospitalization (38 men and 22 women; mean age 56.1 ± 1.3 y.).

Results: Patients of Group B had almost two-fold lower circulating 25(OH)D concentrations than patients of Group A (Group A: 61.6 ± 1.9 nmol/L; Group B: 32.2 ± 1.4 nmol/L; p < 0.001). Within Group A, the only parameter with a statistically significant sex difference was ferritin (p < 0.01). Within Group B, in addition to ferritin (p < 0.05), we observed a pronounced and statistically highly significant sex difference in circulating 25(OH)D concentrations (men: 35.8 ± 1.7 nmol/L; women: 26.0 ± 1.7; p < 0.001).

Conclusions: Our results demonstrate that inadequate vitamin D status is associated with the development of moderate or severe COVID-19 and indicate that circulating 25(OH)D might be associated to sex differences in disease outcome.

Key words: 25(OH)D, SARS-CoV-2, ferritin, women, gender

INTRODUCTION

COVID-19 is a disease that is characterized by high contagiousness and remarkable variability of the clinical presentation. Studies have shown that SARS-CoV-2 initially acts through mechanisms of immune evasion, which in some patients is followed by immune hyper-reaction and cytokine storm, as a common pathogenic mechanism with acute respiratory distress

syndrome and systemic inflammatory distress syndrome, regardless the etiological factor [1]. Studies also indicate a complex interaction between viral infections and vitamin D, including functional immunoregulatory processes, interaction with cellular and viral factors, induction of autophagy and apoptosis, as well as genetic and epigenetic alterations [2]. Accordingly, previous systematic reviews and meta-analyses suggested that vitamin D supplementation significantly reduces the

risk of common upper respiratory tract infections [3,4]. Also, protective role of vitamin D has been shown in many conditions associated with pneumonia, cytokine overproduction and ARDS [1]. Research focused on the role of vitamin D in patients with COVID-19 highlights the importance of optimization of vitamin D status in COVID-19 management [5]. Inadequate vitamin D status in patients with COVID-19 is directly associated with increased concentrations of circulating CRP and IL-6 and increased risk of pneumonia and acute respiratory distress syndrome [6].

In parallel with these observations, another important observation emerged during the COVID-19 pandemic, that is significant sex difference in COVID-19 morbidity and mortality, with male patients having almost three times odds of requiring intensive treatment unit admission and higher odds of death [7].

Based on these observations, we hypothesized that circulating concentrations of 25(OH)D, which is a well-established biomarker of vitamin D status, may be among the key factors associated with marked variability of clinical presentation in patients with COVID-19. Therefore, the aim of this study was to evaluate, at the time of diagnosis of COVID-19, the circulating 25(OH)D concentrations, as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK) and its isoenzyme CK-MB, C-reactive protein (CRP), interleukin 6 (IL-6), white blood cell (WBC) count, erythrocyte sedimentation rate (Se), ferritin (FER), and serum iron (IRN), depending on severity of disease the patients develop, for men and women separately.

METHODS & MATERIAL

Design of this study has been reported in detail previously [8]. In brief, this was a retrospective observational study that was conducted in the General City Hospital "8th September", Skopje, North Macedonia, which, during the most difficult months of the pandemic, was reorganized to operate as a COVID center covering the whole country. The study was conducted from September to December 2020, and was approved by the Ethics Committee of the Hospital. Eligibility criteria for enrolment in this study were the following: adults, at the time of diagnosis of COVID-19 that was confirmed with positive PCR test for SARS-CoV-2, without comorbidities such as diabetes, history of cancer, end-stage kidney disease on hemodialysis, or chronic obstructive lung disease.

Pregnant women were not included in this study. In total, $n = 115$ patients were enrolled and divided in two groups: Group A- asymptomatic or mild cases, $n = 55$ (36 men and 19 women) and Group B- patients who develop moderate or severe COVID-19 requiring hospitalization, $n = 60$ (38 men and 22 women).

Serum concentrations of 25(OH)D were measured using automated immunochemistry analyzer Advia Centaur XP, serum concentrations of CRP and FER were measured using the automated nephelometer BN ProSpec System, serum concentrations of IL-6 were measured using the automated immunochemistry analyzer Immulite 2000 Xpi, and serum concentrations of AST, ALT, GGT, LDH, CK, CK-MB, and IRN were measured using the automated biochemistry analyzer Dimension RxL. WBC count was determined using the automated hematology analyzer Advia 2120i. For all these automated analyzers, original reagents were used. Se was measured using the automated analyzer Alifax.

Statistical data analysis was conducted using the SPSS program.

RESULTS

First, we analyzed the age of patients and found no statistically significant difference between two groups (Group A: 53.3 ± 1.4 y.; Group B: 56.1 ± 1.3 y.; $p > 0.05$), which ruled out potential influence of age on biochemical parameters and severity of disease [9,8]. Next, we showed that serum 25(OH)D concentrations are significantly lower in patients who develop moderate or severe COVID-19 requiring hospitalization, i.e., almost two-fold lower, $p < 0.001$ (Table 1). Comparative analyses of circulating enzymes and biomarkers of inflammatory response in these two groups have been reported previously [9,8].

Table 1. Vitamin D status in patients with COVID-19.

	Group A		Group B	
	Mean \pm standard error	95% Confidence interval for mean	Mean \pm standard error	95% Confidence interval for mean
25(OH)D (nmol/L)	61.5 ± 1.9	57.7 - 65.2	$32.2 \pm 1.4^{***}$	29.5 - 34.9

Group A- asymptomatic or mild cases of COVID-19.

Group B- patients who develop moderate or severe COVID-19 requiring hospitalization.

*** $p < 0.001$

Next, we asked whether there were significant sex differences in the values of analyzed clinical chemistry parameters. To this end, using Mann-Whitney U-test, we analyzed the statistical significance for all parameters depending on gender, i.e., men vs. women, for Group A and Group B separately.

These results showed that in patients of Group A there is a statistically significant sex difference only for FER ($p < 0.01$), while there is almost no difference in serum concentrations of 25(OH)D between men and women (Table 2). Within Group B, a statistically significant difference for FER was also observed ($p < 0.05$). In addition, in patients of Group B a striking sex difference in serum concentrations of 25(OH)D was observed ($p < 0.001$), with women having nearly 10 units lower serum concentrations (Table 3).

Table 2. Vitamin D status, circulating enzymes and biomarkers of inflammatory response in patients with COVID-19; men and women of Group A- asymptomatic or mild cases.

	Men		Women	
	Mean ± standard error	95% Confidence interval for mean	Mean ± standard error	95% Confidence interval for mean
Age (y.)	52.5 ± 1.8	49.0 - 56.1	54.8 ± 2.3 ns	50.0 - 59.6
AST (U/L)	45.1 ± 5.0	35.0 - 55.2	32.3 ± 2.7 ns	26.6 - 37.9
ALT (U/L)	71.6 ± 10.7	49.8 - 93.4	44.5 ± 5.3 ns	33.4 - 55.7
LDH (U/L)	334.7 ± 29.2	275.4 - 394.0	327.0 ± 38.9 ns	245.3 - 408.6
GGT (U/L)	53.6 ± 6.3	40.8 - 66.4	41.5 ± 5.4 ns	30.2 - 52.8
CK (U/L)	226.6 ± 83.8	56.4 - 396.8	90.3 ± 13.3 ns	62.3 - 118.3
CK-MB (U/L)	19.7 ± 1.2	17.2 - 22.2	19.6 ± 1.8 ns	15.8 - 23.4
Se (mm/h)	25.1 ± 2.0	21.0 - 29.3	30.6 ± 3.7 ns	22.8 - 38.5
WBC (x10 ⁹)	6.7 ± 0.4	6.0 - 7.5	7.1 ± 0.6 ns	5.8 - 8.4
CRP (mg/L)	39.1 ± 5.9	27.1 - 51.1	35.3 ± 8.4 ns	17.7 - 52.9
IL-6 (pg/mL)	17.8 ± 3.3	11.0 - 24.5	13.5 ± 3.1 ns	7.1 - 19.9
FER (µg/L)	518.1 ± 54.5	407.5 - 628.7	248.0 ± 53.5**	135.5 - 360.4
IRN (µmol/L)	7.7 ± 0.9	5.9 - 9.5	5.8 ± 0.9 ns	3.9 - 7.8
25(OH)D (nmol/L)	61.6 ± 2.2	57.2 - 66.0	61.3 ± 3.7 ns	53.4 - 69.1

**p < 0.01; ns - nonsignificant; compared to men

Table 3. Vitamin D status and circulating enzymes and biomarkers of inflammatory response in patients with COVID-19; men and women of Group B- patients who develop moderate or severe COVID-19 requiring hospitalization.

	Men		Women	
	Mean ± standard error	95% Confidence interval for mean	Mean ± standard error	95% Confidence interval for mean
Age (y.)	57.8 ± 1.4	55.1 - 60.6	53.1 ± 2.5 ns	47.8 - 58.3
AST (U/L)	54.9 ± 4.8	45.1 - 64.7	54.0 ± 6.3 ns	40.9 - 67.0
ALT (U/L)	68.5 ± 10.0	48.3 - 88.6	56.1 ± 10.9 ns	33.5 - 78.7
LDH (U/L)	449.7 ± 34.9	378.9 - 520.5	420.6 ± 22.6 ns	373.7 - 467.5
GGT (U/L)	101.6 ± 15.5	70.1 - 133.0	90.8 ± 23.5 ns	41.9 - 139.7
CK (U/L)	220.4 ± 42.1	135.2 - 305.6	203.1 ± 58.2 ns	82.0 - 324.1
CK-MB (U/L)	22.4 ± 1.8	18.8 - 26.0	22.8 ± 2.2 ns	18.2 - 27.4
Se (mm/h)	37.8 ± 3.3	31.2 - 44.5	34.2 ± 4.3 ns	25.3 - 43.1
WBC (x10 ⁹)	8.3 ± 0.6	7.1 - 9.5	7.9 ± 0.7 ns	6.4 - 9.4
CRP (mg/L)	93.4 ± 7.9	77.5 - 109.3	112.3 ± 14.9 ns	81.3 - 143.3
IL-6 (pg/mL)	65.8 ± 11.8	41.9 - 89.6	82.3 ± 24.2 ns	32.1 - 132.6
FER (µg/L)	969.2 ± 132.8	700.0 - 1238.3	794.0 ± 271.0*	230.3 - 1357.6
IRN (µmol/L)	5.3 ± 0.5	4.3 - 6.4	4.8 ± 0.7 ns	3.3 - 6.3
25(OH)D (nmol/L)	35.8 ± 1.7	32.4 - 39.2	26.0 ± 1.7 ***	22.5 - 29.4

***p < 0.001; *p < 0.05; ns - nonsignificant; compared to men

DISCUSSION

SARS-CoV-2, the causative pathogen of COVID-19 disease, first emerged in Wuhan, China, in December 2019, and spread with a skyrocket speed all over the world. COVID-19 pandemic, declared by the WHO shortly after, i.e., in March 2020 [10], has resulted in millions of infected people and a significant number of deaths. This situation has led to an overburden of healthcare systems in most countries [11,12], but especially in low- and middle-income countries [13]. About 80% of people who had COVID-19 were asymptomatic or developed only mild symptoms of the disease. The rest of the infected developed a serious

form of the disease [14]. Faced with this serious public health emergency, with no specific drugs or vaccines, drug repurposing was among the first responses suggested by scientists responding to this global crisis [15]. In addition, since the beginning of the pandemic, vitamin D has been highlighted as one of the key factors that determine the course of disease [14]. Suggested putative molecular mechanisms underlying the protective effects of vitamin D in COVID-19 include involvement in maintaining tight junctions, gap junctions, and adherens junctions to decrease viral infection, enhancing cellular innate immunity partly through induction of antimicrobial peptides, reducing the production of pro-inflammatory cytokines, as well as increasing the expression of anti-inflammatory cytokines [16], which led to the recommendation to start using vitamin D to combat COVID-19 that was publicly released as early as on 13 March 2020, Website <https://www.foxnews.com/opinion/former-cdc-chief-tom-frieden-coronavirus-risk-may-be-reduced-with-vitamin-d> (accessed on 28.02.2023).

In addition, since the beginning of the pandemic, a significant sex difference in morbidity and mortality from COVID-19 has been observed [7], with men having a significantly higher mortality than women, approximately 3:1, which indicates the presence of sex-dependent biological factors underlying the observed differences in disease outcome [17]. Suggested putative biological factors include sex-dependent dimorphic immune responses to viral infections [18], sex-dependent modulation of the expression of ACE2 and TMPRSS2, the key proteins for SARS-CoV-2 entrance in human host cells [19], and the protective role of estrogen on the cardiovascular system [20].

Despite significantly lower prevalence, some women still develop a severe form of COVID-19. In this context, the results of our study clearly showed that in patients who develop moderate or severe COVID-19 requiring hospitalization, there was a significant sex difference in circulating 25(OH)D concentrations, with women having particularly pronounced vitamin D deficiency. These results indicate that extreme vitamin D deficiency in women may overcome protective genetic and hormonal factors, leading to a severe form of the disease. This observation derives from the specific, original design of our study and the narrow and well-defined time frame of data collection, which is the period September - December 2020.

The results of our study are in accordance with the

data from the literature [21]. Understandably, at the beginning of the pandemic, reports on the role of vitamin D in COVID-19 were scarce [22,1]. At that time, this role of vitamin D could only be assumed from the existing scientific literature on its immunomodulatory effects [1] as well as from the clinical practice in management of patients with COVID-19 [22]. However, subsequent studies highlighted the role of vitamin D in COVID-19. For example, it has been shown that low 25(OH)D levels assessed at the time of hospitalization are associated with greater COVID-19 severity, requirement for intensive care unit admission, and COVID-19 related mortality [23]. Besides, it has been shown that among hospitalized COVID-19 patients, pre-infection deficiency of vitamin D was associated with increased disease severity and mortality [24]. Also, a recent meta-analysis of thirty-two observational studies has shown that vitamin D deficiency in COVID-19 patients is associated with significantly higher levels of inflammatory biomarkers, such as IL-6, CRP, and FER [25]. In addition, another meta-analysis of twenty-four observational studies showed a potentially increased risk of developing severe COVID-19 infection among patients with low vitamin D levels [26].

In the context of striking sex differences in morbidity and mortality of COVID-19, putative sex differences in protective effects of vitamin D in COVID-19 have also been addressed [27,17]. Previous studies have provided evidence about sex differences in immunomodulatory and anti-inflammatory properties of vitamin D in autoimmune diseases [28], estrogen-dependent vitamin D control of T-cell differentiation [29], or tissue-specific effects of vitamin D on peripheral estrogen and androgen metabolism [30]. However, studies specifically addressing sex-dependent differences in vitamin D status in COVID-19 are rare [31]. To the best of our knowledge, sex difference in circulating 25(OH)D concentrations at the time of diagnosis of COVID-19 in patients who develop moderate or severe COVID-19 requiring hospitalization has not been reported so far. As such, the results of our study represent a foundation for future studies designed to address molecular mechanisms underlying our clinical observation.

In addition to 25(OH)D, we have also observed a significant sex difference for serum FER. Unlike 25(OH)D, a statistically significant sex difference for FER was observed in both Group A and Group B. FER is the major iron storage protein, and as such is essential to iron homeostasis. Low serum FER in otherwise healthy

individuals is highly specific for iron deficiency anemia [32]. On the other side, elevated serum FER occurs not only because of iron overload, but also due to inflammation, liver or kidney disease, cancer, or metabolic syndrome [33]. Accordingly, during the COVID-19 pandemic, serum FER emerged as one of the key inflammatory biomarkers and an important predictor of disease outcome [34]. The results on circulating FER we report here are consistent with the data from the literature, where a sex difference has also been observed, with men having higher mean values than women [35]. This observation can be explained by the sex differences in the reference ranges for this parameter, which are lower for women, but it is also tempting to speculate that the higher circulating concentrations of FER could contribute to the poorer prognosis and worse outcome in men [35].

In conclusion, the outcome of COVID-19 appears to depend on the interaction between genetic and hormonal factors, age and previous comorbidities, and environmental factors that also include, among others, vitamin D status. Our study confirms that inadequate vitamin D status is associated with moderate or severe COVID-19 requiring hospitalization. However, to identify the causal relationships and mechanisms underlying our observation of a significant sex difference in circulating 25(OH)D concentrations in patients who develop moderate or severe COVID-19 requiring hospitalization, additional clinical and basic studies are warranted.

Conflict of interest

The authors declare that they have no conflict of interest.

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