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THE CASUAL ROLE OF VITAMIN D SUPPLEMENTATION IN THE COVID-RELATED HEALTH OUTCOMES (RETROSPECTIVE CROSS-SECTION STUDY)

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D ვიტამინის დანამატების მიზეზობრივი როლის შესწავლა COVID-თან დაკავშირებულ ჯანმრთელობის გამოსავლების ფორმირებაში (რეტროსპექტული ჯვარედინ-სექციური კვლევა)

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რეზიუმე

ჩვენი კვლევის **მიზანს** წარმოადგენდა D ვიტამინის დანამატების მიზეზობრივი როლის შესწავლა COVID-თან დაკავშირებულ ჯანმრთელობის გამოსავლების ფორმირებაში (ჰოსპიტალიზაცია, გადაყვანა ICU განყოფილებაში, ჟანგბადის თერაპიის საჭიროება, მკურნალობა გლუკოკორტიკოიდებით) SARS ინფექციის მქონე პაციენტებში.

მეთოდები. წარმოდგენილი რეტროსპექტული ჯვარედინ-სექციური კვლევა ჩატარდა საქართველოს დაავადებათა კონტროლისა და საზოგადოებრივი ჯანმრთელობის ეროვნული ცენტრის (NCDC) მონაცემებზე დაყრდნობით. კვლევისთვის შემთხვევით შერჩეული იყო 475 პაციენტის ჩანაწერი, რომელთა სისხლის შრატში განსაზღვრული იყო 25-ჰიდროქსივიტამინიD-ს [25(OH)D] დონე. წერილობითი ინფორმირებული თანხმობის მიღების შემდეგ საკვლევ ჯგუფში მოხვდა 384 ადამიანი NCDC მონაცემთა ბაზიდან. კვლევის სუბიექტები დაიყო D ვიტამინის დანამატების მიღების მიხედვით SARS-ვირუსის დადასტურებამდე: ჯგუფი 1 – პაციენტები D ვიტამინის დანამატების მიღებით – n=224; ჯგუფი 2 – პაციენტები D ვიტამინის დანამატების მიღების გარეშე – n=160. პაციენტები გამოკვლეულ იქნენ სპეციალური სტრუქტურირებული კითხვარით, რომლითაც მიღებულ იქნა ინფორმაცია D ვიტამინის დანამატების მიღების შესახებ SARS-ვირუსის დადასტურებამდე.

შედეგები. სისხლის შრატში 25(OH)D-ის საშუალო დონე საკვლევ ჯგუფში 1 იყო 22.5±9.9 ნგ/მლ, ხოლო საკვლევ ჯგუფში 2 იყო 16.9±8.2 ნგ/მლ; ამ მნიშვნელობების სხვაობა ჯგუფებს შორის იყო სარწმუნო - t=5.861, p<0.001. მე-2 ჯგუფში ჰოსპიტალიზაციის შანსები იყო 3.6-ჯერ მეტი 1-ლ ჯგუფთან შედარებით (OR = 3.60, 95%CI 1.85 – 7.03, F-ტესტი = 3.76, p<0.001). ICU განყოფილებაში გადაყვანის (OR = 0.93, 95%CI 0.15 – 5.65, F-ტესტი = 0.08, p=0.939), ჟანგბადის თერაპიის მოთხოვნილება (OR = 1.66, 95%CI 0.86 – 6.65, F-ტესტი = 1.66, p=0.097) და გლუკოკორტიკოიდებით მკურნალობის (OR = 1.41, 95%CI 0.49 – 4.13, F-ტესტი = 0.64, p=0.521) შანსები ჯგუფებს შორის არ იყო სარწმუნო.

დასკვნა. D ვიტამინის დანამატების მიღება ასოცირებული იყო ჰოსპიტალიზაციის 3,6-ჯერ დაბალ რისკთან SARS-CoV-2 ინფექციის გამო. COVID-19-თან დაკავშირებული ავადობა დაკავშირებული იყო შრატში 25(OH)D დონის დაქვეითებასთან. სამომავლო კვლევებმა ასევე უნდა გამოიკვლიოს D ვიტამინის საკმარისი პოტენციური როლი SARS-CoV-2 ინფექციისა და სიკვდილიანობის პრევენციაში. აღსანიშნავია, რომ D ვიტამინის საკმარისობასა და SARS-CoV-2-ის სხვადასხვა შტამებით ინფექციას შორის კავშირი განსაკუთრებულ ყურადღებას მოითხოვს.

Introduction. The COVID-19 pandemic was the outbreak following SARS in 2002 and MERS infections in 2012 [1,2]. However, in contrast to previous ones, COVID-19 has higher transmission rates, and thus incurs more challenges in terms of prevention and treatment [2]. Mortality and other complications were the most susceptible adverse outcomes from COVID-19 [3]. Their risk also increases in the presence of multiple comorbidities such as diabetes, cardiovascular disease, respiratory disease, malignancy and obesity [3-6]. Full recovery of elderly patients who survive COVID-19 took weeks to

months. This led to a fast reduction in muscle mass due to immobilization following hospital discharge, which might lead to an increased risk of frailty, falls, fractures and mortality [7-9].

This susceptible population was likely to suffer from vitamin D deficiency because of the impaired ability to synthetized vitamin D by the skin, limited sun exposure and malabsorption [7,10,11]. In addition, obesity was also highly associated with vitamin D deficiency due to low vitamin D intake, poor dietary habits and alterations in enzymes responsible for vitamin D supplementation [12]. Several reports have suggested a possible association between vitamin D deficiency (25(OH)D levels <20 ng/ml) and COVID-19 susceptibility [13-15]. Although vitamin D is well known for its action on calcium and bone metabolism, extra-skeletal actions have also been described [16]. Particularly, vitamin D plays a role in cytokine release and inflammation, modulation of innate and adaptive immunity, and may decrease the risk of infections via several mechanisms [17-19]. Vitamin D supplementation decreased the risk of acute respiratory infections including influenza infection by 12% overall. Subgroup analyses revealed that daily or weekly doses of vitamin D decrease the risk of infections by 19% compared to placebo, while bolus regimens do not [20]. The same investigators recently confirmed the above results; vitamin D supplementation decreased the risk of respiratory infections by 11%, and doses of 400–1000 IU/day for at least 12 months were the most protective [21]. The effect of vitamin D on other infections is less clear.

Given the above information, experts suggested the possible protective role of vitamin D in the prevention and treatment of COVID-19 infection [7,13,22]. Experts have also published guidance on vitamin D supplementation for its prevention [23-25]. However, such guidance was not based on a systematic review, nor a rigorous synthesis of the evidence. The NICE guideline recommended vitamin D supplementation at a daily dose of 400 IU during the COVID-19 pandemic [26]. In addition, a joint statement, issued from the Endocrine Society, American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), European Calcified Tissue Society (ECTS) and National Osteoporosis Foundation (NOF), recommended a daily dose of 400–1000 IU vitamin D in the COVID-19 pandemic, especially during home isolation for bone protection [27]. These societies do not however recommend supplementation for COVID-19 prevention.

The aim of our study was to investigate the causal role of vitamin D supplementation in the COVID-related health outcomes (hospitalization, transfer to ICU unit, requirement of oxygen therapy, the treatment by glucocorticoids) and clinical characteristics (symptoms) of the patients with SARS infection.

Methods

Study Design and Subjects. Presented retrospective cross-section study was performed based on the data of National Center of Disease control and Public Health (NCDC) of Georgia. 475 records of the patients with determined serum 25-hydroxivitamin D [25(OH)D] levels were randomly selected for the study. Researchers provided the visits of these patients and after obtaining the written informed consent 384 persons from the NCDC database have been included in the study group.

Study Parameters. The data of hospitalization, its duration, transfer to ICU unit, requirement of oxygen therapy, the treatment by glucocorticoids, and symptoms were extracted from the NCDC database. The patients were surveyed by the special structured questionnaires to provide the information about the presence of vitamin D supplementation before the SARS-virus confirmation.

Study Groups. Study subjects were divided by the presence of vitamin D supplementation before SARS-virus was confirmed: the group 1 – patients with vitamin D supplementation – n=224; the group 2 – patients without vitamin D supplementation – n=160.

Statistics. The study results were statistically analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and differences were assessed by analysis of variance. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Odds ratios (ORs) and 95% CIs within the presented study were estimated. P values of <0.05 were considered statistically significant.

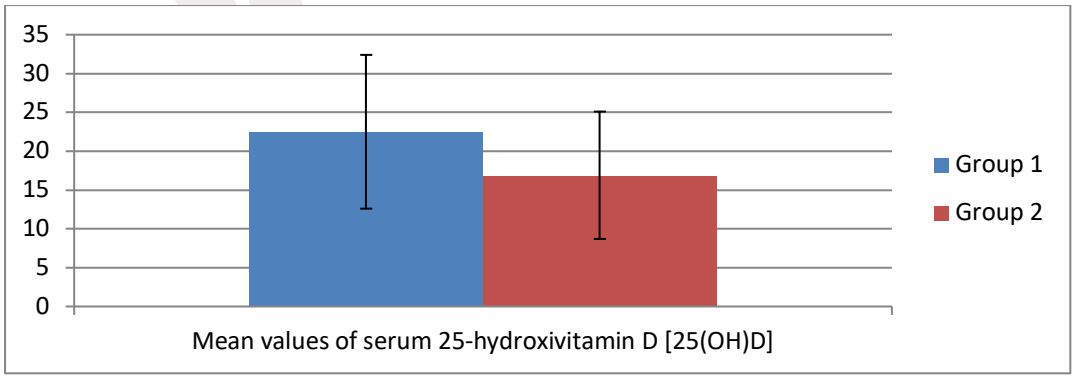
Results. The age, body mass index (BMI) data and the distribution by gender and body weight status of the patients in the study groups are given in Table 1. It is clear from the table that age did not differ between groups significantly. No significant difference was found between the groups according the distribution by the age groups (chi2-test = 1.706, df=2, p=0.426). BMI mean values did not differ significantly between the groups. Same trend was found in the distribution by body mass between the groups – chi2-test = 4.389, df=2, p=0.111. But the distribution by gender was significantly different – Males in the vitamin D supplementation group was significantly lower than in the group 2 (chi2-test = 13.541, df=1, p<0.001).

Table 1. Age, BMI and the distribution of patients by gender and body weight status in the study group

#	Parameter	Group 1 (n=224)		Group 2 (n=160)	
		Mean	SD	Mean	SD
1	Age, years	41.3	19.2	44.2	21.2
2	BMI, kg/m²	26.0	8.0	26.3	4.3
3	Age groups	n=	%	n=	%
	< 30 years	85	37.9%	60	37.5%
	30-49 years	53	23.7%	30	18.8%
	50+ years	86	38.4%	70	43.8%
4	Body Weight Status	n=	%	n=	%
	Normal	98	43.8%	57	35.6%
	Overweight	99	44.2%	73	45.6%
	Obesity	27	12.1%	30	18.8%
5	Gender	n=	%	n=	%
	Males	39	17.4%	54	33.8%
	Females	185	82.6%	106	66.3%

Mean levels of serum 25(OH)D in the study groups are given on Chart 1. The difference of these values between the groups was significant - t=5.861, p<0.001.

Chart 1. Mean levels of serum 25-hydroxivitamin D [25(OH)D]



The data of rates of hospitalization, transfer to ICU unit, the requirement of oxygen therapy, the treatment by glucocorticoids, and SARS-COV-2 infection symptoms were extracted from the NCDC

database are given in Table 2. The odds of hospitalization in the group 2 were 3.6 times higher compared to group 1 (OR = 3.60, 95%CI 1.85 – 7.03, F-test = 3.76, p<0.001). The odds of the requirement of transfer to ICU unit (OR = 0.93, 95%CI 0.15 – 5.65, F-test = 0.08, p=0.939), the requirement of oxygen therapy (OR = 1.66, 95%CI 0.86 – 6.65, F-test = 1.66, p=0.097), and the treatment by glucocorticoids (OR = 1.41, 95%CI 0.49 – 4.13, F-test = 0.64, p=0.521) between the groups were not significant.

Table 2. The distribution of patients by the rates of the hospitalization, transfer to ICU unit, the requirement of oxygen therapy, the treatment by glucocorticoids, and SARS-infection symptoms in the study groups

#	Health outcomes	Group 1 (n=224)		Group 2 (n=160)	
		n=	%	n=	%
1	Hospitalization	**14**	15.6%	**31**	19.4%
2	Transfer to ICU unit	**3**	1.3%	**2**	1.3%
3	Requirement of oxygen therapy	**5**	2.2%	**16**	10.0%
4	Treatment by glucocorticoids	**7**	3.1%	**7**	4.4%

Discussion. There has been a lot of discussion about the impact of vitamin D on SARS-COV-2 infection. vitamin D may alter the disease manifestations depending on its influence on macrophage function and innate immunity. Vitamin D supplementation becomes relevant in the absence of highly effective prevention and treatment strategies for the pandemic. Taking into account the availability and very economic pricing of the drugs, especially in developing countries (countries of Group A and B by Research4Life program [16]) vitamin D supplementation should be an important option for the populations at risk.

Previous systematic reviews have clearly showed an inverse association between 25(OH)D concentration and acute respiratory tract infections [19,20], but these studies were not directly focused on SARS-CoV-2 infection. Similar to our findings, a study from the UK by Panagiotou et al. found that low serum 25(OH)D levels in 134 hospitalized patients with COVID-19 were associated with a more severe disease course [21].

Conversely, a study using the UK Biobank looked at 348 598 participants, of whom only 449 had a confirmed diagnosis of COVID-19 as defined by a positive laboratory test for SARS-CoV-2 (only 0.13% of the study population), and they did not find any association between 25(OH)D and risk of COVID-19 infection [22]. In addition to the low number of patients with COVID-19, other weaknesses in this study included heterogeneity in severity and management of COVID-19 cases (likely a mixture of inpatient and community, instead of focusing on COVID-19 cases in only one setting), serum 25(OH)D measurement between 2006 and 2010, and not contemporaneously with COVID-19 infection 10 to 14 years after recruitment to the UK Biobank, and no mention of validation of 25(OH)D measurement.

In terms of 25(OH)D and COVID-19 disease severity, a study from India of 154 patients admitted to hospital with COVID-19 reported that the mean 25(OH)D level was <30 ng/mL (insufficient range), and patients admitted to the intensive care unit and those that died from COVID-19 were more deficient in vitamin D than survivors [23]. Another study from Belgium (n=186) reported similar findings of greater deficiency rates in patients with more severe disease [24]. Similarly, a study from Switzerland demonstrated that 25(OH)D concentrations were significantly lower in patients with COVID-19 than in those without the disease [25].

Other studies have also demonstrated a correlation between vitamin D deficiency and COVID-19 infection, contrary to the study using patients from the UK Biobank. A study from Israel with 7807 subjects demonstrated that 25(OH)D concentrations were significantly lower among those who tested

positive for COVID-19 than those who were COVID-19 negative [26]. A study from Wuhan, China, showed in a multivariable logistic regression that vitamin D deficiency (<30 nmol/L) was significantly associated with COVID-19 severity [27].

Our study's strengths lie in the usage of relatively recent serum 25(OH)D testing (i.e, carried out within 12 months of inpatient admission with COVID-19), and the use of 2 large cohorts of patients (n=80670 combined). We have clearly demonstrated that vitamin D insufficiency and deficiency exponentially increase the risk of the disease by a factor of 2.3 to 3.6, even after adjustments for age and sex. However, we did not find any association between low 25(OH)D levels or vitamin D status and excess mortality risk, as observed in previous studies [6,8,11,12].

Vitamin D is a pluripotent secosteroid hormone that is important for bone health, but it is also known to regulate cellular functions throughout the body. Vitamin D, specifically, is of 2 types: vitamin D2 (ergocalciferol), derived mainly from plant sources, and vitamin D3 (cholecalciferol), which is present in higher animals and constitutes 80% to 90% of the body's vitamin D [28]. The role of vitamin D in the immune system could partially explain the relationship between vitamin D deficiency and COVID-19 incidence and disease severity. Vitamin D is anti-inflammatory, and it has been shown to modulate the immune system by upregulating a complex set of proteins and inducing the expression of defense peptides such as cathelicidin and β-defensins [29].

Conclusion. Vitamin D supplementation was associated with 3.6-fold lower risk of hospitalization due to SARS-CoV-2 infection. Therefore, COVID-19-related morbidity was associated with the decreased serum 25(OH)D levels. Future studies should also investigate any potential role of vitamin D sufficiency in the prevention of SARS-CoV-2 infection and mortality. Notably, the relation between vitamin D sufficiency and infection with various strains of SARS-CoV-2 requires paying the special attention.

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THE CASUAL ROLE OF VITAMIN D SUPPLEMENTATION IN THE COVID-RELATED HEALTH OUTCOMES. RETROSPECTIVE CROSS-SECTION STUDY

University of Georgia, Tbilisi, Georgia

SUMMARY

The aim of our study was to investigate the causal role of vitamin D supplementation in the COVID-related health outcomes (hospitalization, transfer to ICU unit, requirement of oxygen therapy, the treatment by glucocorticoids) of the patients with SARS infection.

Methods. Presented retrospective cross-section study was performed based on the data of National Center of Disease control and Public Health (NCDC) of Georgia. 475 records of the patients with determined serum 25-hydroxivitamin D [25(OH)D] were randomly selected for the study. Researchers provided the visits of these patients and after obtaining the written informed consent 384 persons from the NCDC database have been included in the study group. Study subjects were divided by the presence

of vitamin D supplementation before SARS-virus was confirmed: the group 1 – patients with vitamin D supplementation – n=224; the group 2 – patients without vitamin D supplementation – n=160. The patients were surveyed by the special structured questionnaires to provide the information about the presence of vitamin D supplementation before the SARS-virus confirmation.

Results. Mean level of serum 25-hydroxivitamin D [25(OH)D] in the study group 1 was 22.5±9.9 ng/ml, and in the study group 2 was 16.9±8.2 ng/ml; The difference of these values between the groups was significant - t=5.861, p<0.001. The odds of hospitalization in the group 2 were 3.6 times higher compared to group 1 (OR = 3.60, 95%CI 1.85 – 7.03, F-test = 3.76, p<0.001). The odds of the requirement of transfer to ICU unit (OR = 0.93, 95%CI 0.15 – 5.65, F-test = 0.08, p=0.939), the requirement of oxygen therapy (OR = 1.66, 95%CI 0.86 – 6.65, F-test = 1.66, p=0.097), and the treatment by glucocorticoids (OR = 1.41, 95%CI 0.49 – 4.13, F-test = 0.64, p=0.521) between the groups were not significant.

Conclusion. Vitamin D supplementation was associated with 3.6-fold lower risk of hospitalization due to SARS-CoV-2 infection. Therefore, COVID-19-related morbidity was associated with the decreased serum 25(OH)D levels. Future studies should also investigate any potential role of vitamin D sufficiency in the prevention of SARS-CoV-2 infection and mortality. Notably, the relation between vitamin D sufficiency and infection with various strains of SARS-CoV-2 requires paying the special attention.

Keywords. COVID-19, Hospitalization, Oxygen Therapy, Glucocorticoids, Vitamin D