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Baseline serum vitamin A and vitamin C levels and their association with disease severity in COVID-19 patients

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Abstract. *Aim:* We aimed to investigate the association between the serum concentrations of Vitamin A and Vitamin C and the severity of the COVID-19. *Methods:* Fifty-three consecutive PCR (+) COVID-19 patients admitted to a dedicated ward were enrolled in this study. Blood samples for serum Vitamin A and C measurements were drawn from all participants upon admission. All subjects underwent thoracic CT imaging prior to hospitalization. CT severity score (CT-SS) was then calculated for determining the extent of pulmonary involvement. A group of healthy volunteers, in whom COVID-19 was ruled out, were assigned to the control group (n=26). These groups were compared by demographic features and serum vitamin A and C levels. The relationship between serum concentrations of these vitamins and pre-defined outcome measures, CT-SS and length of hospitalization (LOH), was also assessed. *Results:* In COVID-19 patients, serum Vitamin A (ng/ml, 494±96 vs. 698±93; p<0.001) and Vitamin C (ng/ml, 2961 [1991-31718] vs. 3953 [1385-8779]; p=0.007) levels were significantly lower with respect to healthy controls. According to the results of correlation analyses, there was a significant negative association between Vitamin A level and outcome measures (LOH, r=-0.293; p=0.009 and CT-SS, r=-0.289; p=0.010). The negative correlations between Vitamin C level and those measures were even more prominent (LOH, r=-0.478; p<0.001 and CT-SS, r=-0.734: p<0.001). *Conclusion:* COVID-19 patients had lower baseline serum Vitamin A and Vitamin C levels as compared to healthy controls. In subjects with COVID-19, Vitamin A and Vitamin C levels were negatively correlated with CT-SS and LOH. (www.actabiomedica.it)

Key words: Ascorbic acid, COVID-19, Hospital stay, Pulmonary disease, Vitamin A

Introduction

COVID-19, caused by SARS-CoV-2, is a multisystem disease primarily affecting the lungs. By April 2022, over 500 million individuals were diagnosed with COVID-19, and over 6 million of the infected population could not survive. Approximately 5% of the cases developed acute respiratory distress syndrome, septic shock, and multi-organ failure (1). Various confounding factors including but not limited to hypertension,

diabetes, smoking, and respiratory and cardiovascular diseases have been reported to predispose COVID-19 which indicated the role of increased pro-inflammatory state and attenuated natural immune response in the pathophysiologic mechanism. Subjects with preexisting pulmonary diseases such as chronic obstructive pulmonary disease, cystic fibrosis, asthma, pulmonary fibrosis, pulmonary hypertension, and pulmonary embolism were particularly more susceptible to serious consequences of COVID-19 (2).

COVID-19 exerted variable clinical presentations ranging from asymptomatic infection to acute respiratory distress syndrome and multi-organ failure among the entire affected population. The host immune response in subjects with COVID-19 has basically 3 phases comprising antiviral defense in the lung parenchyma, awaited local/systemic immune response phase, followed by an uncontrolled inflammatory response, and cytokine storm syndrome (3). The lack of adequate host immune response in subjects infected by SARS-CoV-2 has been shown to be associated with severe infection.

Vitamin A and Vitamin C are micronutrients enhancing both the innate and adaptive immune systems. The therapeutic impact of these molecules in various respiratory infections including COVID-19 was demonstrated (4). Vitamin C was also reported to pose promising effect on alleviating potential complications of the latter (5). However, the relationship between the initial concentrations of these nutrients and the severity of the COVID-19 disease remained debated.

This study aimed to investigate the association between the baseline serum levels of Vitamin A and Vitamin C and COVID-19 disease necessitating hospital admission. The extent of pulmonary involvement and length of hospitalization (LOH) were postulated as the outcome measures representing disease severity.

Materials and methods

Study population

Fifty-three consecutive, PCR (+), COVID-19 patients admitted to a dedicated ward of a tertiary center between May 2020 and July 2020 were enrolled in this cross-sectional study. The ward was specified for patients not showing high-risk clinical features such as high-flow oxygen and positive pressure ventilation requirement, ischemic ECG changes and persistent tachycardia, or hypotension. Patients receiving immunosuppressive agents within the last six months, and those with a history of immunologic or malignant disease were also excluded. The age-matched healthy controls were selected among the candidates exhibiting no symptoms of the disease and those without close contact with individuals who had a verified or possible diagnosis of COVID-19 in the last two weeks. A negative PCR test was also sought for this group. The study was approved by the local ethical committee of Kanuni Sultan Suleyman Hospital (ID: 2020.06.72; Date of approval: 26.06.2020), thus was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants.

Blood sampling

Venous blood samples were drawn from all participants upon admission. Blood samples were collected in heparinized plasma tubes and serum samples were obtained by centrifugation for 10 minutes at 3000 RPM. The samples were conserved in an -80˚C refrigerator which then thawed for executing the assays. Vitamin A (Catalogue number: EA0056Hu, Bioassay Technology Laboratory, China) and Vitamin C (Catalogue number: E1538Hu, Bioassay Technology Laboratory, China) levels were measured in serum samples. Briefly; samples and standards were added to appropriate wells which were pre-coated with Anti-Human monoclonal antibodies to vitamin A and C before incubation. Biotin was added to all wells and combined with Streptavidin-HRP to form an immune complex. Then, re-incubation was performed, and the specimens were rinsed to remove the uncombined enzyme. When Chromogen Solution A and B were added, blue color was generated. The reaction was ceased by adding acid to the plates thereafter which eventually transformed the color into yellow. The optical density was read on a standard automated plate reader at 450 nm (Thermo Scientific Microplate Reader, USA). The detection range of the kits was between 0.8-12.8 ng/mL and 1-300 ng/mL the sensitivities were 0.024 ng/ml

and 0.52 ng/ml for Vitamin A and Vitamin C; respectively.

Chest imaging

All patients underwent a thoracic Computed Tomography (CT) scan prior to hospitalization. A chest CT severity score (CT-SS), developed by Yang et al. was calculated from these images (6). The scale is based on the grading the lung opacification as an equivalent for extension of the disease. Each lung parenchyma is divided into 18 segments and these segments were then split into 20 regions. Each region was scored with 0, 1, or 2 points corresponding to a parenchymal opacification fraction of 0%, 1-50%, or 51-100%, respectively.

Outcome measures representing the disease severity

In this study, we aimed to investigate the relationship between baseline Vitamin A and Vitamin C levels and the surrogate markers of the disease severity which were designated as the CT-SS and LOH for our sample population.

Statistical analysis

Statistical analyses were carried out using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). The distribution of the variables was studied with the Kolmogorov-Smirnov test. Continuous variables were presented as the mean ± standard deviation and categorical variables as a percentage. Student t-test was used for parametric comparisons. The Mann-Whitney U test was used for non-parametric comparisons. The chi-square test was used for the univariate analysis of the categorical variables. Pearson and Spearman correlation analyses were used to test the linear relationship between the vitamin A and C levels and the extent of the pulmonary involvement and LOH. Two-sided $p \leq 0.05$ was interpreted as statistically significant.

Results

A total of 53 COVID-19 patients (age, 30.3±6.5 years) and 26 controls (age, 31.2± 6.4 years) were enrolled in the study. The demographic characteristics including age, body mass index, and concomitant chronic diseases were comparable between the groups. Vitamin A (ng/ml, 494±96 vs. 698±93, p<0.001) and Vitamin C levels ng/ml, (2961 [1385-8779] vs. 3953 [1991-31718], p=0.007) were significantly lower in subjects with COVID-19 as compared to the healthy controls. The mean LOH was COVID-19 patients was 5.9±1.2 days and the mean CT-SS was 16.6±3.7 points (Table 1).

Pearson correlation analysis provided negative significant correlations between Vitamin A level – LOH (r=-0.293, p=0.009) and Vitamin A level – CT-SS (r=-0.289, p=0.010). The Spearman analysis revealed stronger negative correlations between initial

Table 1. Comparison of the demographic characteristics and baseline Vitamin A and C levels between COVID-19 patients and healthy controls.

	Control group (n=26)	COVID-19 group (n=53)	P value
Age, years; Mean±SD	30.3±6.5	31.2± 6.4	0.562
BMI, kg/m^2; Mean±SD	30.6±2.3	30.5±4.6	0±887
Diabetes, n (%)	7 (27)	10 (19)	0.413
Hypertension, n (%)	6 (23)	13 (24)	0.887
Smoking, n (%)	7 (27)	14 (26)	0.962
COPD, n (%)	5 (19)	11 (21)	0.874
Vitamin A, ng/mL; Mean±SD	698±93	494±96	<0.001
Vitamin C, ng/mL; Median (Range)	3953 (1991-31718)	2961 (1385-8779)	0.007

BMI, body mass index; COPD, Chronic obstructive pulmonary disease.

Table 2. Correlations of Vitamin A and Vitamin C levels with the length of the hospital stay and the CT severity score.

	LOH		CT-SS	
	R value	**P value**	**R value**	**P value**
Vitamin A*	-0.293	0.009	-0.478	<0.001
Vitamin C†	-0.289	0.010	-0.734	<0.001

CT-SS, computed tomography severity score; LOH, length of hospitalization. * Pearson test was used for the analysis. † Spearman test was used for the analysis.

Vitamin C level and outcome measures (LOS, r=-0.478; p<0.001 and CT-SS, r=-0.734: p<0.001) (Table 2).

Discussion

This study sought to investigate the relationship between serum Vitamin A and Vitamin C levels on admission and the severity of COVID-19. This study demonstrated that COVID-19 patients confirmed by a positive PCR test had lower Vitamin A and Vitamin C levels as compared to healthy controls. Moreover, both Vitamin C and Vitamin A concentrations significantly correlated with LOH and CT-SS in opposite direction.

The crucial role of host immunity in COVID-19 prognosis has been well-established. It was also clearly identified that an immunocompromised setting is associated with a worse prognosis. As a common reason for acquired immune deficiencies, individuals with malignant disorders were demonstrated to develop serious adverse events more frequently than their immune-competent counterparts during COVID-19 including mortality and assisted-ventilation requirement (7). Similar data were derived from patients with solid organ transplant recipients. Despite the heterogeneity among studies, solid organ transplant recipients with COVID-19 appear to have an increased risk of serious adverse event occurrence and mortality than otherwise healthy individuals (8). Small series enrolling COVID-19 patients with primary immunodeficiency disorders also demonstrated a more severe course as compared to control groups (9). Data concerning patients with HIV infection is currently inconclusive. However, the existing data based on observational studies with limited sample sizes suggested increased COVID-19-associated mortality and morbidity in this subgroup (10,11). In accordance with these data, one should speculate that an adequate immune response is therefore essential not only for refraining from COVID-19 but also for limiting the disease progression.

Both Vitamin A and Vitamin C are micronutrients that have been shown to possess immune-modulating properties. Although the regulatory function of Vitamin A on the immune system has not been fully understood, it is considered to play role in constituting the primary immune defense via altering various pathways of cellular and humoral immune responses. Firstly, Vitamin A is of vital importance for the integrity and continuity of the epithelium, which stands as the first line defense element against the invasion of pathogenic microorganisms. Mucus secretion in the respiratory tract, a mechanistic defense mechanism against pathogenic invasion, is promoted by Vitamin A (12, 13). The resistance of keratinized epithelial tissues against invasion has been shown to decrease in subjects with Vitamin A deficiency (14). Vitamin A is believed to regulate thymic proliferation, where immunocompetent cells are differentiated and matured (15). Both T-cell and antibody-mediated immune responses are reported to be defective in Vitamin A deficient mice (16). Vitamin A also regulates the apoptotic pathways in the bone marrow which provokes the proliferation of the myeloid cells (17).

Vitamin C, an essential micronutrient, also exerts several favorable features on adequate innate and adaptive immune response in addition to its antioxidant effects. Vitamin C aids epithelial barrier function thereby preventing pathogenic invasion as Vitamin A does. Vitamin C also acts as a co-factor for the prolyl- and lysyl-hydroxylase enzymes which maintain the stability of the collagen and enhances the collagen gene expression in fibroblasts (18). Vitamin C supplementation has been shown to improve the epithelial barrier function of lung parenchyma in animal experiments (19). Additionally, the accumulation of Vitamin C in phagocytic cells has been demonstrated to induce chemotaxis and further phagocytosis (20). Vitamin C is also involved in apoptosis and removal

of dysfunctional cellular debris (21, 22). Moreover, Vitamin C facilitates B- and T-cell proliferation (23). Increased production of pro-inflammatory cytokines TNF-α and IL-1α/β and diminished anti-viral cytokine synthesis have been observed in the lung specimens of Vitamin C deficient Gulo knockout mice infected with Influenza virus (24). Improvement of the disease progression and shortened hospital stay was provided by Vitamin C supplementation in individuals with pneumonia (25, 26).

Regarding the abovementioned favorable properties, implementation of Vitamin A and Vitamin C to the prognostic and therapeutic algorithms of COVID-19 were repetitively attempted. Li et al. published the output of their bioinformatics analysis and computation assays in which the potential Vitamin A-associated gene targets against SARS-CoV2 had been investigated. They identified seven core targets. Two of these targets, MAPK1 and EGFR, were also found to be affected by Vitamin C. MAPK1 was featured as a key element of signaling pathways interpreting the external insult to intracellular milieu while the latter was presented as a modulator for cell proliferation and differentiation. These core targets were also speculated to exert a protective effect against pneumonia (27).

Vitamin A deficiency might lead to increased lung injury due to augmented Type I inflammatory response, impaired tissue repair, and diminished immune recall against repetitive exposure to the virus in COVID-19 (28). All-trans retinoic acid, an active metabolite of Vitamin A, plays a regulatory function in mucin production. Mucin is the main component of mucus which constitutes a physical barrier to pathogens (29) Vitamin A was also claimed to exert a protective effect against pulmonary fibrosis (30). Moreover, Vitamin A supplementation was alleged to participate in the enhanced recovery of olfactory function (31). From a different point of view, infections may also culminate in relative Vitamin A deficiency regardless of the dietary intake since retinol-binding protein is acknowledged as a negative acute phase reactant (28).

Similarly, Vitamin C was nominated as a promising nutrient in the adjunctive treatment of COVID-19 since the beginning of the pandemic. In addition to its immunomodulatory, anti-inflammatory effects and several other regulatory functions on oxidative stress and autophagy, Vitamin C poses beneficial features regarding the suppression of concomitant respiratory infectious agents and modifying the risk factors closely associated with COVID-19 prognosis (5). Although mortality benefit or explicit clinical improvement could not be demonstrated in Vitamin C supplementation trials that recruited hospitalized or critically ill patients, reduced risk of thrombotic events and trends towards decreased demand for oxygen and earlier discharge were reported (32,33). Nevertheless, understanding the role of Vitamin A and C in the pathophysiologic process of COVID-19 and revealing the impact of nutrient supplementation on disease progression was not in the scope of this investigation. Instead of verifying a cause-effect relationship between the nutrients of interest and the course of COVID-19, our study was focused on identifying the serum baseline levels of Vitamin A and Vitamin C as prognostic indicators in advanced disease seeking medical attention.

It should be denoted that our study had some limitations to be considered. Firstly, various clinical and laboratory parameters determined as prognostic indicators in COVID-19 were not involved in our study. The therapeutic interventions performed during index hospitalization were not mentioned either. Therefore, a precise independent relationship between the vitamin levels and the ultimate disease outcome could not be constructed. Since COVID-19 patients assigned to this study were followed in a dedicated ward for the ones deemed to exhibit relatively favorable demographic and clinical features, our sample population was younger and had less co-morbidities as compared to patient groups enrolled in similar studies. This was a consequence of an institutional policy which aimed a risk stratification among patients to be admitted. Hence, the staff could be used efficiently in different wards which required alternating level of care mainly by taking their previous familiarity with similar disease scenarios into account. Additionally, advanced statistical analyses could not be applied to the dataset because of the relatively small sample size which could not be further expanded concerning financial constraints.

In summary, our study introduces a novel perspective to the association of Vitamins A and C with COVID-19 necessitating hospitalization. In our sample population, these patients had lower baseline serum Vitamin A and C levels as compared to healthy controls. Furthermore, baseline levels of these nutrients were inversely correlated with disease severity indicated by the CT-SS and LOH. Regarding the low sample size and limited variable spectrum, our study did not have adequate power to point out an independent relationship between vitamin levels and worse outcome. Moreover, low baseline levels of these vitamins might indicate a non-specific host immune response against infection as discussed above. Nevertheless, we speculate that reduced serum levels of these vitamins at the early phase of COVID-19 requiring close in-hospital follow-up is related to a more extensive pulmonary involvement. Unquestionably, this instance can be translated to the anticipation of an extended hospital stay and increased risk of complications such as superimposed bacterial infections, sepsis, and respiratory failure. However, it should be kept in mind that supplementation of the deficient nutrient did not exhibit an evident prognostic improvement in previous trials. Consequently, this reciprocal relationship is yet to be highlighted with various aspects in dedicated larger trials.

This study was conducted in Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey.

Instutitional Ethical Board Approval. Kanuni Sultan Suleyman Training and Research Hospital Local Ethical Committee (Protocol. 2020.06.72, Date of approval. June 2020)

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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