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Retinol Depletion in COVID-19

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SUMMARY

Background and aims: COVID-19 has been a devastating pandemic. There are indications that vitamin A is depleted during infections. Vitamin A is important in development and immune homeostasis. It has been used successfully in measles, RSV and AIDS infections. In this study, we aimed to measure the serum retinol levels in severe COVID-19 patients to assess the importance of vitamin A in the COVID-19 pathogenesis.
Methods: The serum retinol level was measured in two groups of patients: the COVID-19 group, which consisted of 27 severe COVID-19 patients hospitalized in the intensive care unit with respiratory failure, and the control group, which consisted of 23 patients without COVID-19 symptoms.
Results: The mean serum retinol levels were 0.37 mg/L in the COVID-19 group and 0.52 mg/L in the control group. The difference between the serum retinol levels in the two groups was statistically significant. There was no significant difference in retinol levels between different ages and genders within the COVID-19 group. Comorbidity did not affect serum retinol levels.
Conclusion: The serum retinol level was significantly lower in patients with severe COVID-19, and this difference was independent of age or underlying comorbidity. Our data show that retinol

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and retinoic acid signaling might be important in immunopathogenesis of COVID-19.

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1. Background

COVID-19, which is caused by SARS-CoV-2, emerged in December 2019, and was declared a pandemic by the World Health Organization (WHO) in March 2020 [1,2]. So far, by the end of fall of 2021, more than 250 million people have been infected with more than 5 million deaths worldwide [3]. The COVID-19 pandemic causes serious socioeconomic consequences and continues to be a major worldwide health problem [1,2]. Vaccines have been developed for prevention of COVID-19 in an unprecedented speed [4,5]. However, the effectiveness of currently available vaccines varies and immunity they induce declines fast [6,7]. In addition, some vaccines may induce side effects in rare cases [8,9] and some vaccinated people are still getting infected indicating incomplete protection of vaccines [6,10]. Furthermore, emergence of more contagious mutant variants such as delta and omicron has further heightened its public health concerns [6,10]. Even though a couple of antiviral drugs against COVID-19 have recently been developed, their effectiveness needs to be proven [11–13]. Hence, the search for effective and specific anti-COVID-19 drugs and treatment strategies continue throughout the world [14]. Repurposing of existing drugs or identifying effective prevention approaches are important in helping control the spread of COVID-19 and decreasing its devastating impact.

Vitamin A has a seminal role in the development and homeostasis of many organ systems including nervous and immune systems and development of proper immunity against viral infections [15,16]. The protective effects of vitamin A against infections have been known for a long time. The WHO added vitamin A prophylactically to its measles pandemic prevention programs in the 1950s, which achieved successful results and reduced mortality rates due to pneumonia by 50% [17,18]. Retinol has been successfully used in AIDS patients and was effective in decreasing morbidity and mortality due to other viral infections in AIDS [19].

The multi-organ effect of vitamin A is accomplished through retinoic acid signaling, which also has a central and indispensable role in the immune defense mechanism [20–22]. One of the most potent antiviral immune responses is Type-I interferon (IFNα and IFNβ), whose synthesis is regulated through retinoic acid signaling pathway via retinoic acid receptors (RXR and RAR) and transcription factors in Retinoic acid-Inducible Gene-I (RIG-I) pathway [23–26]. Type-I IFN prevents viral replication through recognition of viral RNA and regulation of the host immune system [25]. It activates cytotoxic T cells and induces antibody synthesis by activating B lymphocytes through T helper cells [27,28].

Vitamin A deficiency is associated with deregulated immune response. Vitamin A deficiency causes disruption of mucosal barriers in the gastrointestinal and respiratory systems and a decrease in the number and function of monocytes, macrophages, natural killer cells, and T and B lymphocytes, plasma cells, and antibody response [15,29–31]. Vitamin A deficiency leads to an increased predisposition to infections as well as increased clinical severity of diseases [30,32]. Vitamin A deficiency reduces host resistance to viral infections through impaired interferon production [33–35]. For example, vitamin A deficiency is associated with increased frequency and mortality rates of Measles, Varicella, RSV, AIDS, and viral pneumonia [16,18,31,34].

Infectious diseases can contribute to vitamin A deficiency by suppressing circulatory retinol [36]. In addition, vitamin A stores may become depleted during infections such as measles, RSV, HIV, and viral pneumonia including COVID-19 [34,37–39], leading to an impaired interferon response and causing a vicious infectious cycle [36,40]. As the serum retinol is consumed, it is being supplemented from the large retinol stores in the liver and other body stores [34,39,40]. Therefore, the serum retinol level is reduced only after vitamin A deficiency progresses following depletion of body's large vitamin A stores and detection of low serum retinol level means that retinol stores in the liver have already been

significantly depleted [40]. During systemic infections, high fever also increases metabolic use and urinary excretion and reduces apparent retinol stores [39]. Measles especially disrupts vitamin A metabolism, negatively affecting the use as well as the storage of vitamin A [18,41].

Most immunopathological changes observed in severe COVID-19 patients mimic those of vitamin A deficiency [1,42]. In severe COVID-19 cases, neutrophil and white blood cells are elevated, while total lymphocyte count, CD4 and CD8 positive T cells, regulatory T cells, memory T cells, natural killer and B cells are decreased, as well as antibody synthesis, and thus humoral immunity is also impaired [43–45]. Therefore, retinol depletion and retinoid signaling disorder in COVID-19 may also be responsible for the development of reinfection due to a defect in interferon production, persistence of infection, and insufficient antibody responses after primary infection [34,46,47]. In this study, we aimed to measure retinol level in the serum of COVID-19 and control patients to evaluate the role of retinol and retinoid signaling in the pathogenesis of COVID-19.

2. Material and method

2.1. Patients groups

Fifty patients were stratified into two groups as following: COVID-19 (Group 1, n:27) and Control (Group 2, n:23). COVID-19 group included 27 intensive care unit patients with severe COVID-19 infection with respiratory failure and poor general conditions. The Control group included 23 individuals who were admitted to polyclinics without any COVID-19-related clinical symptoms. The exclusion criteria for both groups were pregnancy, younger than 16 years of age, liver diseases, and taking supplemental vitamin A or retinoic acid three months before admission. Patient characteristics are given in Table 1. COVID-19 RT-PCR test was performed on all patients in the COVID-19 group but not on patients in the Control group. The study was conducted in Gazi Yaşargil Training and Research Hospital, Diyarbakir, Turkey between July and August of 2020. The study protocol was approved by the Ethics Committee of the University of Health Sciences, Diyarbakir Gazi Yaşargil Training and Research Hospital, and the Ministry of Health of Turkey (dated June 3, 2020, and numbered T22_10_40. xml). The study was conducted according to the approved protocols following all recommendations and regulations of the local ethics committee and in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Diet and treatment

Nutrition solutions administered to the patients were determined retrospectively. No diet restriction was applied to conscious patients who could be fed orally. These patients continued to eat regular hospital meals. However, twelve patients in the COVID-19 group, who could not be fed orally, were fed

Table 1
General characteristics of patients in COVID-19 and control groups

	n	Sex (F+M)	Notes	Comorbidities
COVID-19	27	14+13	• All severe COVID-19 ICU patients • COVID-19 positivity confirmed with RT-PCR • 25 received Favipiravir • 2 received Hydroxychloroquine • 10 received supplemental nutrition including multivitamin • 8 had various comorbidity • 12 deceased during study	• High blood pressure [6] • Type II diabetes [3] • Chronic kidney disease [2] • Asthma [1] • Heart disease [1] • Hypothyroidism [1] • Peripheral vascular disease [1] • Surrenal fibrosis [1] (3 patients had 3 or more comorbid diseases each, 3 patients had 2 comorbid diseases each, and 2 patients had 1 comorbid disease each)
Control	23	15+8	• Polyclinic patients but without any COVID-19 symptoms	

through a nasogastric tube or parenteral route using various nutritional formulas containing poly-unsaturated fatty acid (omega 3) and multivitamins including vitamin A and vitamin D (supplemental material).

The COVID-19 group continued receiving (due to ethical concerns) the drugs containing the active ingredient of Favipiravir and hydroxychloroquine that were used for the treatment of COVID-19. Favipiravir is inhibitor of RNA dependent RNA polymerase of various RNA viruses [44]. Hydroxychloroquine is an inhibitor of lysosomal pathway and autophagy and is traditionally used for treatment of malaria [45, 46]. It also inhibits cytochrome oxidase P450 enzymes in the liver and therefore prevents hepatic retinol excretion [47].

2.3. Measurement of serum retinol level

The venous blood samples taken from the patients were transferred to light-proof tubes. The tubes were covered with aluminum foil to protect vitamin A from light. The blood samples were kept undisturbed at room temperature for 30 minutes and then centrifuged at 1000g. The collected serum samples were kept at -80ºC until the levels of retinol were measured. Retinol in serum samples was analyzed using High-Performance Liquid Chromatography method (Agilent 1200 Series HPLC System, USCN Life Science, Wuhan, China). The level of serum retinol was calculated in mg/L and the level below 0.2 mg/L was considered low per WHO recommendation [48,43].

2.4. Measurement of serum ferritin level

The serum ferritin level was determined with immunoassay using Cobas e601 (Roche diagnostics, Germany).

2.5. Blood lymphocyte counts

Blood lymphocyte count was performed using Mindray BC 6800 (Mindray Building, High-Tech Industrial Park, Nanshan, Shenzhen China).

2.6. Statistical analysis

The statistical analysis of data was performed using IBM SPSS 22.00 for Windows program (Statistical Package for Social Sciences, Chicago, IL, USA). The Shapiro-Wilk Test was used to test for the normal distribution of the data. All data in all groups, except for ferritin level in the control group, were compliant with the normality assumption. The Mann-Whitney U Test was used to assess the significance of differences between the groups and between subgroups within COVID-19 group. In all statistical analysis, the $P<0.05$ was considered statistically significant.

3. Results

3.1. Serum retinol level was significantly lower in the COVID-19 group

The mean serum retinol level was 0.37 mg/L in the COVID-19 patient group (SD=+/-0.15) and 0.52 mg/L in the control group (SD=+/-0.09). The difference in the retinol levels between the two groups was statistically significant ($P<0.001$) (Table 2). However, no significant difference was found in retinol levels between the female and male subgroups within COVID-19 group ($P>0.05$) (Table 2).

3.2. Patients in the COVID-19 group were significantly older

The average age of the patient in the COVID-19 group was 63.2 years, while that of the control group was 44.8 years. The age difference between the two groups was statistically significant ($P<0.001$) (Table 2). To correct for the age-related variability of retinol levels, the patient group was stratified into two age subgroups with cut-off of 60 years of age: 60 years of age and under (N=10) and over 60 years of

Table 2
The retinol levels and age in the COVID-19 and Control groups

	Group	Group	n	Mean	Median	SD	Min	Max	*P**	*P***
Retinol (mg/L)	COVID-19	M+F	27	0.37	0.38	0.15	0.14	0.76	-	<0.001
		F [14]		0.34	0.35	0.10	0.15	0.46	>0.05	
		M [13]		0.41	0.39	0.19	0.14	0.76		
	Control	M+F	23	0.52	0.53	0.09	0.29	0.67	-	
		F [15]		0.53	0.53	0.06	0.46	0.62	>0.05	
		M [8]		0.50	0.51	0.14	0.29	0.67		
Age (year)	COVID-19	M+F	27	63.26	63	15.93	32.00	91.00	-	<0.001
		F [14]		66.71	69	16.99	32	91	>0.05	
		M [13]		59.54	60	14.44	32	91		
	Control	M+F	23	44.83	43	14.87	35	81	-	
		F [15]		42.27	37	14.84	22	75	>0.05	
		M [8]		49.63	51	14.66	22	72		

*P** denotes *P* values for the female and male subgroups within each group. P** denotes *P* values for main COVID-19 and control groups.

age (N=17). The difference in the serum retinol levels between these two age subgroups within the COVID-19 patient group was not statistically significant (*P*> 0.05) (Table 3). The mean serum retinol level was 0.38 mg/L in the group with 60 years of age and below (SD=+/-0.21) and 0.36 mg/L in the group of above 60 years of age (SD=+/-0.12).

3.3. Drug use and nutritional supplementation

In the COVID-19 group, 25 patients received Favipiravir and 2 received hydroxychloroquine. Despite the use of these drugs, their retinol levels were still significantly lower compared to those of the control group (*P*< 0.001). Ten patients in the COVID-19 group were given various nutritional supplements, some of which also contained vitamin A (supplemental material). Even though the average retinol level in the group that received nutritional supplement was higher, this difference was not statistically significant (*P*>0.05).

3.4. Comorbidity and exitus

Ten of 27 patients in COVID-19 group received nutritional supplement. Nine of these 10 patients (90%) died, and 8 of these 9 patients also had another comorbid disease that posed a high risk for morbidity and mortality (Table 1). Three of the 17 patients who did not receive nutritional supplement died. There was a statistically significant correlation between nutritional supplement and death rate (*P*<0.001). However, this correlation seems to be due to comorbidities and not due to the nutritional supplementation as 8 out of 9 patients had comorbidities. No significant difference was found in serum retinol levels between these two groups. Twelve of 27 patients in the COVID-19 group died. There was no significant difference in retinol levels between those who died and those who were discharged (*P*>0.05).

3.5. Ferritin levels and lymphocyte counts

The serum ferritin level and lymphocyte counts were also evaluated. Ferritin levels were found high and lymphocyte counts were found low in the COVID-19 group compared to the control group

Table 3
Retinol levels in the sub-age groups in the COVID-19 group

Group	Age (year)	n	Serum retinol (mg/L) (mean/median) (+/-SD) (min-max)	Deceased	*P*-value
COVID-19	≤60	10	0.38/0.40 (+/-0.21) (0.14–0.76)	3	>0.05
	>60	17	0.36/0.37 (+/-0.12) (0.15–0.67)	9	

*P** denotes *P* values for above and below 60 years of age subgroups within COVID-19 group.

Table 4
Serum Ferritin level and lymphocyte counts

	Group	n	(Mean/median) (+/-SD) (min-max)	*P*-value
Ferritin (mg/L)	COVID-19	27	(1086.26/965) (+/-651.03) (186–2100)	<0.001
	Control	20	(98.75/62.50) (+/-109.25) (4–406)	
Lymphocyte count (10^3/mL)	COVID-19	27	(1.15/0.98) (+/-0.64) (0.30–3.27)	<0.001
	Control	21	(2.89/2.87) (+/-0.95) (1.18–4.71)	

(Table 4). These findings were compliant with the findings of clinical studies in the literature and were associated with poor prognosis in COVID-19 [50,51].

4. Discussion

Even though the size of our study is small, our results show a correlation between serum retinol level and severe COVID-19 infection, which supports the retinol depletion and retinoid signaling defect theory that we previously postulated for the pathogenesis of COVID-19 [49,50]. Despite the continuous use of Favipiravir and hydroxychloroquine, both of which inhibit retinol metabolism through inhibiting CYP450 enzymes, and the presence of vitamins including vitamin A in the administered nutritional formulations, the serum retinol level was significantly lower in severe COVID-19 cases. Even though this observation shows association of low serum retinol level with the severity of COVID-19, it may well have some causative effect in which low level of serum retinol may lead the way to a more inflammatory immune response that may in turn cause development of a severe immunopathophysiology seen in the severe COVID-19 cases [49–51]. However, this interesting observation needs further investigation.

Our results support the previous studies that COVID-19 is more severe in elderly patients [2,52]. Since the average age of severe COVID-19 patients in our study was higher, we tested whether the age might affect the serum retinol level by stratifying the COVID-19 patients according to the age. We did not find a significant difference in retinol levels between the age subgroups, younger versus older than 60 years of age. It seems that the difference in retinol levels between the COVID-19 group and the control group is not directly related to age, but could be caused by the COVID-19 infection itself.

Twelve patients in the COVID-19 group died. It is likely that the death of these patients was contributed to by their comorbid diseases and that the low level of vitamin A, despite supplementation, did not provide any protective help. It is tempting to argue that a possible very low level of vitamin A and retinoic acid at the beginning of the infection might have allowed an increased inflammation and the severe disease pathogenesis.

Our data show no significant differences in the serum retinol levels between the patients with and without comorbidity within the COVID-19 group. We expected low vitamin A levels in the comorbid group due to the inflammatory processes of chronic diseases. Some comorbid patients taking nutritional supplement that also contained vitamin A might have affected this result.

It is important to note that due to the limited resources and urgency of some clinical data early during COVID-19 pandemic, our study size was kept very small. A limitation of our study might be that it is possible, even though less likely that any asymptomatic COVID-19 patients that might have been in the control group would have skewed our results since we did not perform RT-PCR test due to resource limitations.

Supplementation of vitamin A in the administered fortified nutrition mix did not seem to influence the serum retinol level despite slightly increasing it. This may be due to the low doses of vitamin A in the nutritional supplement and high rate of consumption due to severe disease pathology. Studies show that the effect of vitamin A use is dose-dependent and high doses should be used before or at the beginning of the infection before the severe inflammatory process involve multi-organ damage as it is also the case for vitamin D [53–56]. Likewise, vitamin A may suppress excessive inflammatory processes only at normal serum levels and at the therapeutic doses [34,49,57].

Vitamin A has a similar effect as vitamin D in the COVID-19 pathology as both vitamins involve retinoid signaling in regulating proper immune response. The role of vitamin D has been recognized in the treatment of COVID-19 at high enough doses [58–60]. Vitamin D is effective in mild to moderate

COVID-19, whereas failure to respond to vitamin D supplementation in severe COVID-19 may be due to vitamin A depletion. Because nuclear steroid hormone receptors, including the vitamin D receptor, act as heterodimeric receptors in complex with the retinoid X receptor (RXR). Therefore, deficiency in vitamin A and D may perturb retinoid signaling which then may lead to skewed immune response. The RXR receptor is needed not only for vitamins A and D, but also for other steroid compounds to have an effect. [61,62].

The reason why the regulation mechanism of endogenous retinoic acids has not been noticed until now in COVID-19 may be the assumption that retinoic acid, an endogenous retinoid signaling ligand, can always be present in the body. However, the amount of retinoic acid in the human body is limited and is sufficient for approximately three months for a person [63,64]. Serum retinol levels drop only after the deficiency has progressed to severe levels and the large-scale stores of vitamin A in the liver are depleted, and by the time the serum retinol levels are found to be low, the liver retinol stores will already be largely depleted [65]. Retinol and retinoic acids can be rapidly depleted due to reasons such as excessive viral load, high fever, and catabolic destruction, especially with continuous and long-term RIG-I stimulation [64,66].

STRA6, the receptor that take vitamin A into the cells, has recently been reported to be a receptor, in addition to ACE, for the spike protein of SARS-CoV2 to infect cells [67]. It will be interesting to know how the use of retinol receptor by the virus might affect vitamin A internalization and metabolism as well as its immunoregulatory function.

We anticipated that retinoic acid excretion might have been lower in women than in men due to the estradiol effect. Estradiol inhibits many more enzymes within the CYP450 system than testosterone, which inhibits only CYP2D6 [66,68,69]. The CYP450 system is less suppressed in men than in women [70,71]. Based on this role of estradiol on CYP450 enzymes, we expected higher retinol levels in women than in men. However, our results show no significant difference in retinol levels between male and female subgroups. We believe this may have been affected by the low number of cases, the non-homogeneity of the patient group, the use of CYP450 inhibitory drugs, and the administration of dietary supplements containing vitamin A to the patients. A well-controlled larger study shall yield more reliable results about the difference in retinol metabolism between men and women in COVID-19.

If some specific enzymes of the CYP450 system are inhibited, the metabolism of retinoic acids will also be inhibited, raising intracellular RA levels reaching to the therapeutic levels. For this purpose, agents that block the metabolism of retinoic acids, called RAMBAs (retinioic acid metabolism blocking agents) have been developed [72–75]. Early treatment with such inhibitors in COVID-19 may increase endogenous retinoic acid levels by preventing retinoic acid metabolism in liver [72]. Thus, in COVID-19, Type-I interferon can be synthesized early during infection, and the virus can be cleared from the body without worsening the disease pathogenesis [27,76]. Recent molecules docking and genome wide association studies on the pathogenesis of COVID-19 points to the importance of retinol and retinoic acid signaling [67,77–79]. Detailed understanding of the pathogenesis of COVID-19 will increase our ability to develop prophylactic and treatment options for COVID-19.

5. Conclusion

While COVID-19 may be mild or asymptomatic in some people, it may be very serious in some others. We think that this clinical difference is highly correlated with the state of retinol stores in the body. Malnutrition, comorbid diseases, chronic lung and liver diseases, obesity, hepatosteatosis, chronic inflammation, febrile diseases, and excessive antigenic stimulation all may cause depletion of retinol stores and weaken immune defense against pathogens including SARS-CoV-2 (49, 65). A sufficient level of retinol and retinoic acid may help generate type-I interferon response to SARS-CoV-2 infection [80]. Even though small, our study found that serum retinol levels were significantly low in patients with severe COVID-19. Given the potential for many overlooked factors to affect retinol levels, prospective clinical studies with larger, more carefully selected case groups are needed to identify the role of vitamin A or retinoids in COVID-19 treatment. Such studies will also shed light on the detailed pathogenesis of COVID-19 and provide guidelines for COVID-19 treatment and prophylaxis.

However, even though the lack of vitamin A has serious health consequences, overdose of retinol and retinoids will cause serious consequences [81–83]. Therefore, retinol and carotenoids may be

supplemented to the vitamin A deficient individuals. However, the use of retinoids and ATRA for treatment or prophylaxis must be under the supervision of medical professionals to evade the toxic effect of overdosing of vitamin A.

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Author contributions

ARS conceived, created, and reviewed the literature, and wrote the project, protocol, and manuscript. HA selected patient and screened patient files. EA involved in official submission and follow-up of the protocol to the ethics committee. ÖA performed the statistical analysis of the data. OC reviewed literature, discussed, revised, re-organized, and re-wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest. No author is affiliated with any undeclared institution or financial relationship that could affect the objectivity of this study.

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Appendix A. Supplementary data

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References

[1] Olwenyi OA, Dyavar SR, Acharya A, Podany AT, Fletcher CV, Ng CL, et al. Immuno-epidemiology and pathophysiology of coronavirus disease 2019 (COVID-19). J Molecul Med (Berlin, Germany) 2020;98(10):1369–83.
[2] Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses 2020;12(4).
[3] WHO. WHO coronovirus (COVID-19) dashboard [website]. World Health Organization; [updated 12/09/2021. Available from: https://covid19.who.int/.
[4] Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: The status and perspectives in delivery points of view. Adv Drug Delivery Rev 2021;170:1–25.
[5] Krammer F. SARS-CoV-2 vaccines in development. Nature 2020;586(7830):516–27.
[6] Farooqi T, Malik JA, Mulla AH, Al Hagbani T, Almansour K, Ubaid MA, et al. An overview of SARS-COV-2 epidemiology, mutant variants, vaccines, and management strategies. J Infect Pub Health 2021;14(10):1299–312.
[7] Mandell BF. A perspective on discussing COVID-19 vaccines: Efficacy and adverse effects. Cleveland Clinic J Med 2021; 88(12):644–5.
[8] Capone F, Lucchini M, Ferraro E, Bianco A, Rossi M, Cicia A, et al. Immunogenicity and safety of mRNA COVID-19 vaccines in people with multiple sclerosis treated with different disease-modifying therapies. Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics 2021:1–9.
[9] D'Agostino V, Caranci F, Negro A, Piscitelli V, Tuccillo B, Fasano F, et al. A Rare Case of Cerebral Venous Thrombosis and Disseminated Intravascular Coagulation Temporally Associated to the COVID-19 Vaccine Administration. J Personal Med 2021;11(4).
[10] Mohamed K, Rzymski P, Islam MS, Makuku R, Mushtaq A, Khan A, et al. COVID-19 vaccinations: The unknowns, challenges, and hopes. J Med Virology 2021.
[11] Barnabas RV, Brown E, Bershteyn A, Miller RS, Wener M, Celum C, et al. Efficacy of hydroxychloroquine for post-exposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among adults exposed to coronavirus disease (COVID-19): a structured summary of a study protocol for a randomised controlled trial. Trials 2020; 21(1):475.
[12] Lee CC, Hsieh CC, Ko WC. Molnupiravir-A Novel Oral Anti-SARS-CoV-2 Agent. Antibiotics (Basel, Switzerland) 2021;10(11).
[13] Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ (Clinical Research Ed) 2021;375:n2713.

[14] Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharmaceutica Sinica B 2020;10(5):766–88.
[15] Stephensen CB. Vitamin A, Infection, and Immune Function. Annual Review of Nutrition 2001;21(1):167–92.
[16] Sommer A. Vitamin A, infectious disease, and childhood mortality: a 2 solution? J Infect Dis 1993;167(5):1003–7.
[17] Benn CS. Combining vitamin A and vaccines: convenience or conflict? Danish Med J 2012;59(1):B4378.
[18] Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. The Cochrane Database of Systematic Reviews 2005;(4):Cd001479.
[19] Mehta S, Fawzi W. Effects of vitamins, including vitamin A, on HIV/AIDS patients. Vitamins and Hormones 2007;75:355–83.
[20] Al Tanoury Z, Piskunov A, Rochette-Egly C. Vitamin A and retinoid signaling: genomic and nongenomic effects. J Lipid Res 2013;54(7):1761–75.
[21] Ghyselinck NB, Duester G. Retinoic acid signaling pathways. Development (Cambridge, England) 2019;146(13).
[22] Elias KM, Laurence A, Davidson TS, Stephens G, Kanno Y, Shevach EM, et al. Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway. Blood 2008;111(3):1013–20.
[23] Cassani B, Villablanca EJ, De Calisto J, Wang S, Mora JR. Vitamin A and immune regulation: role of retinoic acid in gut-associated dendritic cell education, immune protection and tolerance. Molecular Aspects of Medicine 2012;33(1):63–76.
[24] Trottier C, Chabot S, Mann KK, Colombo M, Chatterjee A, Miller Jr WH, et al. Retinoids inhibit measles virus in vitro via nuclear retinoid receptor signaling pathways. Antiviral Research 2008;80(1):45–53.
[25] Liu Y, Olagnier D, Lin R. Host and Viral Modulation of RIG-I-Mediated Antiviral Immunity. Frontiers in Immunology 2016;7:662.
[26] Samuel CE. Antiviral actions of interferons. Clinical Microbiology Reviews 2001;14(4):778–809. table of contents.
[27] Garbe A, Buck J, Hämmerling U. Retinoids are important cofactors in T cell activation. J Experiment Med 1992;176(1):109–17.
[28] Takeuchi H, Yokota-Nakatsuma A, Ohoka Y, Kagechika H, Kato C, Song SY, et al. Retinoid X receptor agonists modulate Foxp3$^+$ regulatory T cell and Th17 cell differentiation with differential dependence on retinoic acid receptor activation. J Immunol (Baltimore, Md : 1950) 2013;191(7):3725–33.
[29] McGill JL, Kelly SM, Guerra-Maupome M, Winkley E, Henningson J, Narasimhan B, et al. Vitamin A deficiency impairs the immune response to intranasal vaccination and RSV infection in neonatal calves. Scientific Reports 2019;9(1):15157.
[30] Ross AC. Vitamin A and retinoic acid in T cell-related immunity. American J Clinic Nutri 2012;96(5). 1166s-72s.
[31] Sirisinha S. The pleiotropic role of vitamin A in regulating mucosal immunity. Asian Pacific J Allerg Immunol 2015;33(2):71–89.
[32] Ross AC, Stephensen CB. Vitamin A and retinoids in antiviral responses. FASEB Journal 1996;10(9):979–85.
[33] Lee H, Ko G. Antiviral effect of vitamin A on norovirus infection via modulation of the gut microbiome. Scientific Reports 2016;6:25835.
[34] Stephensen CB, Lietz G. Vitamin A in resistance to and recovery from infection: relevance to SARS-CoV2. British J Nutri 2021:1–10.
[35] Chattha KS, Kandasamy S, Vlasova AN, Saif LJ. Vitamin A deficiency impairs adaptive B and T cell responses to a prototype monovalent attenuated human rotavirus vaccine and virulent human rotavirus challenge in a gnotobiotic piglet model. PloS One 2013;8(12):e82966.
[36] Campos FA, Flores H, Underwood BA. Effect of an infection on vitamin A status of children as measured by the relative dose response (RDR). American J Clinic Nutri 1987;46(1):91–4.
[37] Ni J, Wei J, Wu T. Vitamin A for non-measles pneumonia in children. Cochrane Database System Rev 2005;2005(3):Cd003700.
[38] Gudas LJ. Emerging roles for retinoids in regeneration and differentiation in normal and disease states. Biochimica et Biophysica Acta 2012;1821(1):213–21.
[39] Arroyave G, Calcaño M. Decrease in serum levels of retinol and its binding protein (RBP) in infection. Archivos Latinoamericanos de Nutricion 1979;29(2):233–60.
[40] Wiseman EM, Bar-El Dadon S, Reifen R. The vicious cycle of vitamin a deficiency: A review. Critical Reviews in Food Science and Nutrition 2017;57(17):3703–14.
[41] Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. Cochrane Database System Rev 2017;3(3):Cd008524.
[42] Mortaz E, Tabarsi P, Varahram M, Folkerts G, Adcock IM. The Immune Response and Immunopathology of COVID-19. Frontiers in Immunology 2020;11:2037.
[43] Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. Annals of Hematology 2020;99(7):1421–8.
[44] Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. Cell 2020;183(4):996–1012.e19.
[45] Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. Immunology 2020;160(3):261–8.
[46] Sa Ribero M, Jouvenet N, Dreux M, Nisole S. Interplay between SARS-CoV-2 and the type I interferon response. PLoS Pathogens 2020;16(7):e1008737.
[47] Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Reports 2020;33(1):108234.
[48] WHO. Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations. WHO report; 2011.
[49] Sarohan AR, Kızıl M, İnkaya A, Mahmud S, Akram M, Cen O. A novel hypothesis for COVID-19 pathogenesis: Retinol depletion and retinoid signaling disorder. Cellular Signalling 2021;87:110121.
[50] Sarohan AR. COVID-19: Endogenous Retinoic Acid Theory and Retinoic Acid Depletion Syndrome. Medical Hypotheses 2020;144:110250.

[51] Sarohan AR. Systemic Organ Involvement and Retinoid Signaling Disorder in COVID-19. Immunogenetics: Open Access 2021;6(3):1–6.
[52] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmunity 2020;109:102433.
[53] Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of Vitamin A in the Immune System. J Clinic Med 2018;7(9).
[54] Raverdeau M, Mills KH. Modulation of T cell and innate immune responses by retinoic Acid. J Immunol (Baltimore, Md: 1950) 2014;192(7):2953–8.
[55] Meltzer DO, Best TJ, Zhang H, Vokes T, Arora VM, Solway J. Association of Vitamin D Levels, Race/Ethnicity, and Clinical Characteristics With COVID-19 Test Results. JAMA Network Open 2021;4(3):e214117.
[56] Vyas N, Kurian SJ, Bagchi D, Manu MK, Saravu K, Unnikrishnan MK, et al. Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects. J American College Nutri 2020:1–14.
[57] Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. Nutrients 2020;12(6).
[58] Li Y, Tong CH, Bare LA, Devlin JJ. Assessment of the Association of Vitamin D Level With SARS-CoV-2 Seropositivity Among Working-Age Adults. JAMA Network Open 2021;4(5):e2111634.
[59] Mansur JL, Tajer C, Mariani J, Inserra F, Ferder L, Manucha W. Vitamin D high doses supplementation could represent a promising alternative to prevent or treat COVID-19 infection. Clinica e Investigacion en Arteriosclerosis : Publicacion Oficial de la Sociedad Espanola de Arteriosclerosis 2020;32(6):267–77.
[60] Allegra A, Tonacci A, Pioggia G, Musolino C, Gangemi S. Vitamin deficiency as risk factor for SARS-CoV-2 infection: correlation with susceptibility and prognosis. European Rev Med Pharmacol Sci 2020;24(18):9721–38.
[61] Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and Novel Actions. Annal Nutri & Metabol 2018;72(2):87–95.
[62] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. Jama 2021;325(11):1053–60.
[63] Balmer JE, Blomhoff R. Gene expression regulation by retinoic acid. J Lipid Res 2002;43(11):1773–808.
[64] Ross AC, Zolfaghari R. Cytochrome P450s in the regulation of cellular retinoic acid metabolism. Annual Rev Nutri 2011;31:65–87.
[65] Wolf G. Retinoic acid homeostasis: retinoic acid regulates liver retinol esterification as well as its own catabolic oxidation in liver. Nutri Rev 2001;59(12):391–4.
[66] Pelkonen O, Rautio A, Raunio H, Pasanen M. CYP2A6: a human coumarin 7-hydroxylase. Toxicology 2000;144(1–3):139–47.
[67] Elkazzaz M, Ahmed AKK, Shamkh IM, Abo El Magd MF. STRA6 (Vitamin A receptor), as a Novel binding receptor of COVID-19. ScienceOpen Preprints.
[68] Usmani KA, Tang J. Human cytochrome P450: metabolism of testosterone by CYP3A4 and inhibition by ketoconazole. Current Protocols in Toxicology 2004 [Chapter 4]:Unit4.13.
[69] Rogers AS. The role of cytochrome P450 in developmental pharmacology. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 1994;15(8):635–40.
[70] Sverko A, Sobočanec S, Kušić B, Mačak-Šafranko Z, Sarić A, Leniček T, et al. Superoxide dismutase and cytochrome P450 isoenzymes might be associated with higher risk of renal cell carcinoma in male patients. Int Immunopharmacol 2011;11(6):639–45.
[71] Dhir RN, Dworakowski W, Thangavel C, Shapiro BH. Sexually dimorphic regulation of hepatic isoforms of human cytochrome p450 by growth hormone. J Pharmacol Experiment Therapeut 2006;316(1):87–94.
[72] Nelson CH, Buttrick BR, Isoherranen N. Therapeutic potential of the inhibition of the retinoic acid hydroxylases CYP26A1 and CYP26B1 by xenobiotics. Current Topics in Medicinal Chemistry 2013;13(12):1402–28.
[73] Njar VC, Gediya L, Purushottamachar P, Chopra P, Vasaitis TS, Khandelwal A, et al. Retinoic acid metabolism blocking agents (RAMBAs) for treatment of cancer and dermatological diseases. Bioorganic & Medicinal Chemistry 2006;14(13):4323–40.
[74] Purushottamachar P, Patel JB, Gediya LK, Clement OO, Njar VC. First chemical feature-based pharmacophore modeling of potent retinoidal retinoic acid metabolism blocking agents (RAMBAs): identification of novel RAMBA scaffolds. European J Med Chem 2012;47(1):412–23.
[75] Verfaille CJ, Borgers M, van Steensel MA. Retinoic acid metabolism blocking agents (RAMBAs): a new paradigm in the treatment of hyperkeratotic disorders. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 2008;6(5):355–64.
[76] Trasino SE. A role for retinoids in the treatment of COVID-19? Clinic Experiment Pharmacol & Physiol 2020;47(10):1765–7.
[77] Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. New England J Med 2020;383(16):1522–34.
[78] Nakanishi T, Pigazzini S, Degenhardt F, Cordioli M, Butler-Laporte G, Maya-Miles D, et al. Age-dependent impact of the major common genetic risk factor for COVID-19 on severity and mortality. medRxiv; 2021.
[79] Elkazzaz MR, Abo-Amer YE-E, Ahmed A, Haydara T. Could the candidate causal gene (LZTFL1) identified by Oxford University scientists, which doubles the risk of COVID-19-related respiratory failure, be used to boost the Weak immunogenicity of COVID-19 mRNA vaccines in patients with B-cell chronic lymphocytic leukemia (CLL)???. A double edged sward. Pre-print of an intended journal article ed2021..
[80] Van YH, Lee WH, Ortiz S, Lee MH, Qin HJ, Liu CP. All-trans retinoic acid inhibits type 1 diabetes by T regulatory (Treg)-dependent suppression of interferon-gamma-producing T-cells without affecting Th17 cells. Diabetes 2009;58(1):146–55.
[81] Broulík PD, Raška I, Brouliková K. Prolonged overdose of all-trans retinoic acid enhances bone sensitivity in castrated mice. Nutrition (Burbank, Los Angeles County, Calif) 2013;29(9):1166–9.
[82] Piersma AH, Hessel EV, Staal YC. Retinoic acid in developmental toxicology: Teratogen, morphogen and biomarker. Reproductive Toxicology (Elmsford, NY) 2017;72:53–61.
[83] Russell RM. The vitamin A spectrum: from deficiency to toxicity. American J Clinic Nutri 2000;71(4):878–84.