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Research Article

The role of DBP gene polymorphisms in the prevalence of new coronavirus disease 2019 infection and mortality rate

Short Title: rs7041 and rs4588 polymorphisms in COVID-19

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Abstract

Since December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has given rise to emerging respiratory infections with a pandemical diffusion. The vitamin D binding protein (DBP) with emphasis on its regulation of total and free vitamin D metabolite levels in various clinical conditions. The main goal of this study was to evaluate if there is any

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association between the DBP gene polymorphism at rs7041 and rs4588 loci and the prevalence of COVID-19 and its mortality rates caused among populations of ten countries including Turkey. Positive significant correlations were found between the prevalence (per million) and mortality rates (per million), and GT genotype ($p < 0.05$) while there was a negative significant correlation between prevalence (per million) and mortality rates (per million), and TT genotype at *rs7041* locus among all populations ($p < 0.05$). However, no significant correlation was found at *rs4588* locus. GT genotype was found to confer this susceptibility to the populations of Germany, Mexico, Italy, Czech and Turkey. The variations in the prevalence of COVID-19 and its mortality rates among countries may be explained by Vitamin D metabolism differed by the DBP polymorphisms of *rs7041* and *rs4588*.

Keywords: coronavirus disease 2019, vitamin D binding protein, polymorphism, rs7041, rs4588

1 Introduction

Since December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has given rise to emerging respiratory infections with a pandemical diffusion.[1] By July 2, 2020, the global number of confirmed cases of COVID-19 reached 10,534,765 with a mortality of 512,881.[2] In Turkey, 201,098 cases and 5150 deaths have been confirmed until 2nd July 2020.[2] There has recently found a relationship between vitamin D levels and the number COVID-19 cases and the mortality rates caused by the coronavirus infection.[3]

The vitamin D binding protein (DBP) with emphasis on its regulation of total and free vitamin D metabolite levels in various clinical conditions. Nearly all DBP is produced in the liver, where its regulation is influenced by estrogen, glucocorticoids and inflammatory cytokines but not by vitamin D itself. DBP is the most polymorphic protein known, and different DBP alleles can have substantial impact on its biologic functions.[4] The two most common alleles—Gc1s (*rs7041* locus) and Gc2 (*rs4588* locus)—differ in their affinity with the vitamin D metabolites and have been variably associated with several clinical conditions.[4] Among these conditions, G allele at the *rs7041* locus was found to be related with increased susceptibility to hepatitis C viral infection.[5] Moreover, the individuals having an AA genotype within *rs4588* locus of the Gc2 polymorphic region showed a greater increase in 25(OH)D levels following vitamin D supplementation than those with the GG genotype have.[6] A single nucleotide polymorphism at *rs4588* have been associated with susceptibility to the metabolic syndrome.[7] Therefore, we hypothesized that DBP polymorphisms may play a significant role for COVID-19.

The main goal of this study was to evaluate if there is any association between the DBP gene polymorphism at *rs7041* and *rs4588* loci and the prevalence of COVID-19 and its mortality rates caused among populations of ten countries including Turkey.

2 Materials and Methods

To test this hypothesis and to limit confounding bias (latitude, etc.), we focused on the countries whose DBP polymorphisms at rs7041 and rs4588 loci were defined and the allele frequencies were reported in five cohort and two systematic review and meta-analysis studies.[8-15] We searched the literature for DBP gene polymorphism in each country. We recorded the total number of cases of COVID-19 and per million population in each of the countries to find the prevalence, and the mortality rates caused by the Coronavirus infection recorded at 2nd July 2020 (Table 1) according to WHO Coronavirus disease (COVID-19) Situation Report – 164.[2]

The allele frequencies of DBP polymorphisms at rs7041 and rs4588 loci of Turkish population were retrieved from a previous thesis study (unpublished results).[16] The ethical approval for analyzing the blood samples to examine the polymorphisms was obtained from Biruni University Non-Interventional Research Ethics Committee (Approval No: 2017/10-1). The written consent forms were obtained from all subjects who were informed about the study.

Blood samples were collected from 51 healthy Turkish individuals who applied for check-up, met the study criteria and agreed to participate in the study. The selection criteria were not using any vitamin D supplements for last two years, not having any health problem that would affect the vitamin D concentrations and not being a black person. Total 25(OH)D concentrations were measured by a chemiluminescence microparticle immunoassay method (CMIA), using Architect 25-OH Vitamin D kit (5P02, Abbott Diagnosis, USA) and i1000SR analyser (Abbott Laboratories, USA).

DNA isolation from whole blood was performed by quick-DNATM miniprep plus (Zymo Research, USA) DNA isolation kit. Isolated DNAs were stored at -200°C for further analysis. DNA quality and concentration measurements were performed in 2µl DNA with NanoDrop 2000c spectrophotometer (Thermofisher Scientific, USA). Using isolated genomic DNA, genotyping for the most common SNPs of DBP, rs4588 and rs7041, was performed by using TaqMan probes for real-time PCR. The SNP assay coded by C_8278879_10 (Applied Biosystems TaqMan SNP Genotyping Assays Thermo Fisher Scientific, USA) was used for genotyping rs4588, and SNP assay coded by C_3133594_30 (Thermo Fisher Scientific) was used for genotyping rs7041. The base sequences were CTTGTTAACCAGCTTTGCCAGTTCC*[G/T]TGGGTGTGGCATCAGGCAATTT

TC and CTTTGCCAGTTCCGTGGGTGTGGC*[A/C]TCAGGCAATTTTGCTTTTAGTCGT, respectively. Real-time temperature cycle reaction conditions were adjusted according to the protocol of manufacturer and literature.[17]

All data were analyzed by SPSS (statistical package for social sciences) for Windows 22 program. In the analysis of the data, first the assumptions that must be met were tested to decide which tests (parametric / nonparametric tests) to apply. Shapiro Wilk test, kurtosis and skewness values which are other assumptions of normal distribution, and histogram graph were used to decide the normality of the distribution. Considering the insufficient number of data in each group, it was decided that the data did not exhibit normal distribution. The relationship between independent variables was examined with Spearman correlation coefficient (rho). In the interpretation of whether the obtained values are significant or not, 0.05 significance level was used as a criterion.

3 Results

The mean age of 51 healthy individuals from Turkish population was 39,39 ± 12,30. 49.1% of individuals were male (n =25) and 50.9% were female (n = 26). The mean concentration of total 25(OH)D was 20.75 ± 14.2 ng/ml.

Population diversities of *rs7041* polymorphisms showed that the populations of China, Japan, Nigeria and Kenya mostly have TT genotype while the populations of Germany, Mexico, Italy, Czech and Turkey mostly have GT genotype (Table 1). Population diversities of *rs4588* polymorphisms revealed that the populations of all countries except Finland and Turkey mostly have CC genotype while Finn and Turkish populations have AC genotype at *rs4588* locus. The prevalence of COVID-19 and mortality rates per country recorded at 2nd July 2020 showed that Germany, Mexico, Italy and Turkey had the highest number of COVID-19 cases and mortality rates per million of the populations of countries involved in the study (Table 1).

Correlation between *rs7041* and *rs4588* polymorphisms and prevalence of COVID-19 and mortality rates per country demonstrated that there were positive significant correlations between the prevalence (per million) and mortality rates (per million), and GT genotype ($p < 0.05$) while there was a negative significant correlation between prevalence (per million) and mortality rates (per million), and TT genotype at *rs7041* locus among all populations ($p < 0.05$). However, no significant correlation was found between the prevalence (per million) and mortality rates (per million), and the polymorphism at *rs4588* locus (Table 2).

4 Discussion

In the present study, TT genotype was found to confer COVID-19 susceptibility to the populations of China, Japan, Nigeria and Kenya. GT genotype was found to confer this susceptibility to the populations of Germany, Mexico, Italy, Czech and Turkey. The variations in the prevalence of COVID-19 and its mortality rates among countries may be explained by Vitamin D metabolism differed by the DBP polymorphisms of *rs7041* and *rs4588*.

DBP is the most polymorphic protein known which regulates the total and circulating free vitamin D metabolite levels in various clinical conditions. DBP alleles differ in their affinity with the vitamin D metabolites and can have substantial impact on various clinical conditions.[4] Polymorphisms in the DBP gene has been reported to be associated with Vitamin D deficiency in different populations.[12,18,19] The general prevalence of vitamin D deficiency varies in the world, ranging from 7% to 77%.[20]

Vitamin D deficiency is more common in the subtropical (including China) and mid-latitude (including Italy, Japan, Turkey) countries than the tropical (Mexico, Nigeria and Kenya) and high-latitude countries.[21] In a study conducted in 1161 healthy subjects from Turkish population, Ozturk et al. found the overall mean serum 25(OH)D level as 16.61 ± 6.90 ng/ml and reported a high prevalence of vitamin D insufficiency or deficiency in all age groups. They also showed that the vitamin D deficiency is very common (75.54% with 25(OH)D< 20 ng/ml) among adult Turkish population.[22] Totally, these studies implicate the vitamin D levels are mainly regulated by the genetic background of both healthy population and patients. In the present study, the genetic variations in DBP gene, specifically SNP in *rs7041* locus, were found to be correlated with the prevalence of COVID-19 and mortality rates among countries.

Previous studies have identified a potential common relationship between the mean vitamin D levels in various European countries with COVID-19 cases per million population and its mortality.[3,23] Ilie et al. reported negative correlations between mean levels of vitamin D in European countries including Turkey and the number of COVID-19 cases per million population.[3] They suggest that Spain, Italy and Switzerland are the most vulnerable group of the population in relation to COVID-19 since the vitamin D levels are severely low in the aging population especially in these countries. They explained the crude association by the role of vitamin D in the prevention of COVID-19 infection or more probably by a potential protection of vitamin D from the more negative consequences of the infection.[3]

Vitamin D plays a major role regulating the immune system, including immune responses to viral infection.[24] Interventional and observational epidemiological studies provide evidence that vitamin D deficiency may confer increased risk of influenza and respiratory tract infection.[25] Cell culture experiments support the thesis that vitamin D has direct anti-viral effects particularly against enveloped viruses. Though vitamin D's anti-viral mechanism has not been fully established, it may be linked to vitamin D's ability to up-regulate the anti-microbial peptides LL-37 and human beta defensin 2.[26] Regarding the genetic susceptibility to a viral infection in vitamin D deficiency, we also observed significant correlations between *rs7041* polymorphism and prevalence of COVID-19 and mortality rates per country. However, no significant correlation was found between the prevalence (per million) and mortality rates (per million) at *rs4588* locus.

The pathology of COVID-19 involves a complex interaction between the SARS-CoV2 and the body immune system. Calcitriol (1,25-dihydroxyvitamin D3) exerts pronounced impacts on ACE2/Ang(1–7)/MasR axis with enhanced expression of ACE2.[27] ACE2 is the host cell receptor responsible for mediating infection by SARS-CoV-2. ACE2 polymorphisms were recently described in human populations.[28] Another common polymorphism was found in DBP gene which is highly polymorphic gene. Allelic variants of DBP gene have been studied extensively for their association with vitamin-D deficiency,[29,30] and viral infections.[5] Two of these variants corresponding to different allelic arrangements of rs7041 and rs4588 were reported to have a different affinity to bind to vitamin-D3, hence affect its serum concentration.[31] Different DBP isoforms influence the serum concentration/bioavailability of vitamin-D3.[9] From this perspective these isoforms might be correlated with an increased risk of viral infection in populations, as reported in the present study. If a necessary concentration of bioavailable vitamin D is not reached in certain genotypes, the immune system may modulate the body reaction to an infection in a severe way.

Low levels of total vitamin D, which are more common in black than in white, are associated with negative health outcomes in epidemiologic studies.[32-34] Powe et al. reported lower mean levels of both total vitamin D and DBP in blacks than in whites due to the genetic polymorphisms.[34] Among homozygous participants, blacks and whites had similar levels of bioavailable vitamin D. Therefore, racial differences in the prevalence of common genetic polymorphisms provide a likely explanation for altered Vitamin D metabolism. In the present study, the genetic polymorphism especially in *rs7041* locus of DBP gene is probably associated with the increased risk of COVID-19 infection and its mortality among populations with white race.

Vitamin D deficiency is known to impair the ability of macrophages to mature, to produce macrophage-specific surface antigens, to produce the lysosomal enzyme acid phosphatase, and to secrete H2O2, a function integral to their antimicrobial function.[35] Vitamin D has been also reported to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokines,[36] which are frequently observed in COVID-19 cases.[37] Therefore, the correlation of the variations in DBP polymorphisms and the prevalence of COVID-19 with its mortality rate may depend on the modulatory effect of bioavailable Vitamin D levels of individuals which is determined by the genetic background. However, the prevalence of SARS COV-2 infection differs from the severity of COVID-19, by association with many factors such as public awareness, behaviors and antiviral policy of each country except the host genetic factors. On the contrary, the severity of the disease induced by viral infection might be associated with the genetic host factors. More detailed and large sampled studies about the genetic variations in infected patients with different degrees of severity are needed to explain the underlying mechanism of Vitamin D metabolism in COVID-19 patients.

Data Availability Statement

The data related to COVID-19 that support the findings of this study are available in Coronavirus disease (COVID-19) Situation Report – 164 of World Health Organization, at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200702-covid-19-sitrep-164.pdf?sfvrsn=ac074f58_2.

The data of 51 healthy Turkish individuals that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure of Conflicts of Interest

None

5 References

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Table 1 Population diversities of rs7041 and rs4588 polymorphisms, prevalence of COVID-19 and mortality rates per country recorded at 2nd July 2020

	rs7041			rs4588			Prevalence[1]		Mortality[1]		
Country	*GG*	*GT*	*TT*	*AA*	*AC*	*CC*	*Total*	*per million*	*Total*	*per million*	*Reference*
China	7.30	42.3	50.4	8.8	44.9	46.3	81263	59.24	4648	3.23	Zhou *et al.*
Japan	8.80	31.9	59.3	2.7	43.8	53.6	18874	149.23	975	7.71	Khanna *et al.*
Nigeria	0.70	15.6	83.7	0.0	8.20	91.8	26484	128.48	603	2.93	Khanna *et al.*

Kenya	0.90	12.7	86.4	0.9	11.0	88.1	6673	124.1	149	2.77	Jones *et al.*
Mexico	24.1	50.0	25.9	1.8	46.4	51.8	226089	1753.54	27769	215.38	Rivera-Paredez *et al.*
Italy	25.5	56.9	17.6	5.9	39.2	54.9	240760	3982.01	34788	575.37	Jones *et al.*
Turkey	31.0	49.0	20.0	2.0	53.0	45.0	201098	2384	5150	61.06	Present data
Finland	63.6	32.5	3.9	10.8	48.7	40.5	7236	1305.81	328	59.19	Enlund-Cerullo *et al.*
Germany	31.9	48.2	19.9	8.7	42.0	49.3	194725	2323.56	8985	107.21	Terock *et al.*
Czechia	38.8	49.4	11.9	6.2	42.5	51.2	12046	1124.69	349	32.58	Pleva *et al.*

1 Recorded on 2nd July 2020 from *WHO Coronavirus disease (COVID-19) Situation Report – 164*

Table 2. Correlation between rs7041 and rs4588 polymorphisms and prevalence of COVID-19 and mortality rates per country

Spearman's rho		GG	GT	TT	AA	AC	CC
Prevalence per million	r	0.61	0.73	-0.*62*	0.12	0.27	-0.25
	p	0.06	**0.02**	**0.04**	0.75	0.45	0.49
Mortality per million	r	0.*60*	0.87	-0.66	0.27	0.*36*	-0.31
	p	0.07	**0.01**	**0.04**	0.*45*	0.31	0.38