Int J Clin Exp Pathol 2015;8(7):8463-8471
www.ijcep.com /ISSN:1936-2625/IJCEP0009995

Original Article

Association between promoter region genetic variants of PTH SNPs and serum 25(OH)-vitamin D level

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Received May 7, 2014; Accepted June 23, 2015; Epub July 1, 2015; Published July 15, 2015

Abstract: Parathyroid hormone (PTH) plays a crucial role in calcium metabolism and skeletal development via altering vitamin D level. Besides, hypersecretion of PTH is implicated in the etiology of osteoporosis. In this study, we analyzed association between promoter region sequence variants of PTH gene and circulating 25-hydroxy-vitamin D (25(OH)D) level. Genotypes of PTH SNPs rs1459015, rs10500783 and rs10500784 and circulating serum 25(OH)D level of healthy adults (N=386) of different nationalities living in Riyadh were determined and relation between the different PTH allelic variants and corresponding mean 25(OH)D values were obtained using Analysis of Variance (ANOVA) and Bonferroni post-hoc test for multiple comparisons. We observed a high prevalence of vitamin D deficiency (<50 nmol/l) among all nationals which ranged from 59% among Indians to 82% among Yemeni. Comparison of the means of 25(OH)D levels corresponding to different genotypes of PTH SNPs indicated that the T allele of SNP rs1459015 was associated with higher 25(OH)D level in the Sudanese (P=0.03), while the T allele of SNP rs10500783 was associated with higher 25(OH)D level in Saudis (P=0.03). Analysis of results also indicated that the Sudanese carriers of the CC genotype of SNP rs1459015 had a higher risk of suffering from vitamin D deficiency (P=0.02). In conclusion, our study indicated significant association between specific PTH gene promoter region variants and altered levels of 25(OH)D and vitamin D deficiency among specific nationals.

Keywords: Parathyroid hormone, vitamin D, 25(OH)D, single nucleotide polymorphism, osteoporosis

Introduction

Vitamin D is the common denominator of a group of sterols with crucial roles in calcium and phosphorus metabolism and immune function regulation [1, 2]. Most of vitamin D is obtained from the conversion of 7-dehydrocholesterol to pre-vitamin D3 in the skin by means of solar ultraviolet B radiation, while a smaller fraction is contributed by diet. Vitamin D deficiency is one of the most common medical conditions worldwide with more than 1 billion children and adults at risk [3]. Vitamin D deficiency is associated with adverse health outcomes which include increased risk of osteoporosis, falls and fractures [4, 5]. Results from clinical trials and epidemiological studies have linked low plasma 25-hydroxy-vitamin D (25(OH)D) to various disease conditions such as obesity, metabolic syndrome, type 2 diabetes, respiratory and cardiovascular diseases and cancer [6-9].

Vitamin D3 undergoes 25-hydroxylation in the liver and the resulting 25(OH)D, the main circulating form of vitamin D, is used to determine the vitamin D status of a given individual. Lips classified a level of 25(OH)D above 50 nmol/l (20 ng/ml) as normal and 26-50 nmol/l (10-20 ng/mL) as mild, 12.5-25 nmol/l (5-10 ng/mL) as moderate and <12.5 nmol/l (<5 ng/ml) as severe deficiencies [10]. High prevalence of vitamin D deficiency has been found in various populations across geographic and ethnic types [11]. Recently, there has been a lot of focus on various factors that determine the level of vitamin D.

PTH regulates and maintains calcium and phosphate levels within a certain homeostatic range

[12]. High PTH is associated with hyperparathyroidism, which may be a) due to problems in the glands themselves, in which case it is referred to as primary hyperparathyroidism, or b) a response to low calcium levels, as encountered in various situations such as vitamin D deficiency or chronic kidney disease, which is referred to as secondary hyperparathyroidism [13]. High PTH, mostly due to tumors of the parathyroids, leads to hypercalcaemia by increasing bone resorption. Under normal physiological conditions lack of vitamin D leads to reduced calcium absorption by the intestine causing hypocalcaemia and secondarily increased parathyroid hormone production [14]. PTH upregulates renal 1-α-hydroxylase, which converts 25-hydroxycholecalciferol to the active form of vitamin D, 1, 25-dihydroxy vitamin D [15]. Hence, there is an important role for PTH in maintaining the concentration of the active vitamin D.

Ethnicity has been found to affect the relationships between 25(OH)D, bone mineral density, and PTH among US adults [16]. Polymorphisms in the promoter and coding regions of the PTH gene may affect the production and functionality of PTH, respectively. Since significant differences have been detected in the level of vitamin D among different ethnic groups, this study was designed to explore the association between the various genotypes of PTH SNPs and 25(OH)D levels. We studied PTH SNPs rs1459015, rs10500783 and rs10500784 located ~5 kb, 56 kb and 56.2 kb, respectively, upstream of the PTH coding sequence.

Previous studies have demonstrated that 25(OH)D levels in Saudi citizens were lower than rest of the world [17, 18], even though Saudi Arabia enjoys a sunny climate throughout the year. Saudi Arabia has experienced heavy international immigration in the last three decades, and Riyadh, capital of Saudi Arabia, hosts an immigrant population composed of people from different parts of world and hence was considered an ideal place to assess the influence of ethnicity on vitamin D level. The aim of this study was to assess the prevalence of vitamin D deficiency in a population-based survey of randomly recruited adults belonging to five different nationalities living in Riyadh, Saudi Arabia, and to explore for association, if any, between 25(OH)D levels and genetic variants of PTH SNPs.

Methodology

Subjects

The study involved 386 healthy volunteers (males=154, females=232), aged between 20-60 years. The participants were classified according to their nationalities: Egyptian (N=123), Sudanese (N=97), Yemenis (N=90) and Indian (N=49), in addition to Saudis (N=27). The volunteers were restricted from taking any kinds of medications affecting bone metabolism for one month before being screened. Written and informed consents were taken before inclusion in the study. Ethics approval was granted by the Ethics Committee of the College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia (KSA). Participating subjects were recruited and enrolled longitudinally in four primary health care centers (PHCCs) within the Riyadh Central Region. They were asked to complete a generalized questionnaire, containing demographic information including past and present medical history, and to return next morning after fasting for more than 10 hours for anthropometric measurements and blood withdrawal.

Anthropometry and blood collection

Subjects were requested to visit their respective PHCCs following overnight fasting (>10 hours) for anthropometry and blood withdrawal. Anthropometry included height (rounded off to the nearest 0.5 cm), weight (rounded off to the nearest 0.1 kg), waist and hip circumference (centimeters), and mean systolic and diastolic blood pressure (mm Hg) (average of 2 readings). Body mass index was calculated as weight in kilograms divided by height in square meters. Fasting blood samples were collected and transferred immediately to a non-heparinized tube for centrifugation. Collected serum was then transferred to pre-labeled plain tubes, stored in ice and delivered to the Biomarkers Research Program (BRP) in King Saud University, Riyadh, KSA, for immediate storage at -20°C.

Biochemical analyses

Fasting glucose, lipid profile, calcium, and phosphorous were measured using a chemical analyzer (Konelab, Espoo, Finland). Serum 25(OH)D was measured by Roche Elecsys mod-

Table 1. Anthropometric and biochemical characteristics of the study population by nationality

	Yemeni	Sudanese	Indian	Egyptian	Saudi	*P*
N	90	97	49	123	27	
Age (years)	35.4 ± 12.6	37.5 ± 12.1	37.3 ± 10.4	31.7 ± 15.1[b]	33.5 ± 12.6	0.01
BMI (kg/m^2)	27.2 ± 6.3	28.3 ± 5.8	27.6 ± 4.7	28.6 ± 7.3	29.4 ± 5.1	NS
Waist (cm)	89.6 ± 15.7	93.7 ± 17.1	94.6 ± 11.5	88.1 ± 12.3	91.3 ± 18.2	NS
Hips (cm)	105.9 ± 14.9	104.5 ± 19.6	100.8 ± 13.2	101.3 ± 14.3	109.8 ± 16.8	NS
SAD (cm)	26.5 ± 4.2	27.1 ± 3.2	26.3 ± 2.6	27.3 ± 3.6	28.6 ± 3.7	NS
Systolic BP (mm Hg)	121.1 ± 16.1	120.5 ± 16.4	121.9 ± 10.8	120.7 ± 13.7	116.9 ± 14.6	NS
Diastolic BP (mm Hg)	76.0 ± 9.2	77.3 ± 9.3	78.8 ± 8.7	77.8 ± 9.4	75.4 ± 10.2	NS
T. Cholesterol (mmol/l)	4.6 ± 0.94	4.7 ± 1.0	4.8 ± 0.96	4.5 ± 1.0	5.2 ± 1.2[d]	0.03
Triglycerides (mmol/l)	1.5 ± 0.23	1.7 ± 0.21	2.2 ± 0.26[a]	1.5 ± 0.30[c]	1.6 ± 0.32	0.01
HDL-C (mmol/l)	1.1 ± 0.35	1.0 ± 0.29	0.86 ± 0.21[a]	1.1 ± 0.32[c]	1.2 ± 0.33[b,d]	<0.001
LDL-C (mmol/l)	3.3 ± 0.90	3.3 ± 0.87	3.5 ± 0.85	3.2 ± 0.91	3.5 ± 0.92	NS
Vitamin D (nmol/l)	29.1 ± 1.8	31.4 ± 1.6	41.3 ± 1.6[a,b]	38.0 ± 1.6[a]	35.3 ± 1.7	<0.001
Vitamin D deficiency (%)	82.2	80.4	59.2	66.7	70.4	0.007
Ca (mmol/l)	2.3 ± 0.20	2.3 ± 0.19	2.1 ± 0.11[a,b]	2.4 ± 0.24	2.3 ± 0.24	<0.001
Corrected Ca (mmol/l)	2.3 ± 0.17	2.3 ± 0.16	2.1 ± 0.11[a,b]	2.4 ± 0.22[c]	2.4 ± 0.16[c]	<0.001

a-Significantly different from Yemenis; b-significantly different from Sudanese; c-significantly different from Indians; d-significantly different from Egyptian.

ular analytics Cobas e411 using Electrochemiluminescence immuno assay (Roche Diagnostics, GmbH, Mannheim, Germany) using commercially available kits. It is noted that although the BRP laboratory did not participate in the Vitamin D External Quality Assessment Scheme (DEQAS), Quality Assurance (QA) standards are maintained by ISO 9000 and 17025, and the QA department audits the BRP laboratory at regular intervals.

Genotyping PTH SNPs

Whole blood was collected in EDTA-containing tubes and genomic DNA extracted using Blood Genomic Prep Mini-spin Kit (GE Healthcare). DNA was stored at -20°C until analyzed. The three PTH SNPs (rs1459015, rs10500783 and rs10500784) were evaluated by allelic discrimination Real-time PCR using pre-designed TaqMan probes (Applied Bio systems, Foster City, CA, USA). The PCR consisted of hot-start at 95°C for 10 minutes followed by 50 cycles of 94°C for 15 seconds and 60°C for 1 minute. All assays were performed in 15 µl reactions, using TaqMan Genotyping Master Mix on 96-well plates using CFX96 Real Time PCR instrument (Bio-Rad). Control samples representing all possible genotypes and a negative control were included in each reaction.

Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA). Normality was checked using Kolmogorov Smirnov test. All Non-Gaussian parameters were either log or square root transformed. Normal continuous variables were presented as mean ± standard deviation. Variables were compared among different nationalities and genotypes using Analysis of Variance (ANOVA), followed by Bonferroni post-hoc test for multiple comparisons. Independent sample Student t-test was also used to compare two groups. Odds ratios [95% Confidence Interval (CI)] vitamin D deficiency risk among different allele carriers were defined by multinomial logistic regression. Significance was set at $P \leq 0.05$.

Results

A cross-sectional study was performed on 386 adults. Anthropometric and biochemical characteristics of the study population by respective nationalities are shown in **Table 1**. Ages ranged between 31.7 and 37.5 years, with a mean age of 34.9 ± 13.2 years. The composition of the study subjects were: 7.1% Saudis, 31.8% Egyptians, 12.7% Indian, 25.1% Sudanese, and 23.3% Yemenis. The mean body

Table 2. Association between genotypic variants of PTH SNPs and anthropometric and biochemical characteristics

	rs1459015				rs10500783				rs10500784			
	TT	CT	CC	*P*	TT	CT	CC	*P*	CC	AC	AA	*P*
N	26	138	222		25	62	299		21	54	369	
BMI (kg/m^2)	27.6 ± 6.3	28.1 ± 5.6	28.3 ± 6.7	NS	26.2 ± 5.2	29.7 ± 6.1	27.9 ± 6.3	0.05	32.6 ± 8.2	28.7 ± 5.8	28.1 ± 6.3	NS
Waist (cm)	92.1 ± 17.1	92.0 ± 14.1	91.0 ± 20.0	NS	87.8 ± 19.7	93.2 ± 15.8	91.2 ± 18.8	NS	104.0 ± 22.6	94.2 ± 12.4	90.9 ± 19.4	NS
Hips (cm)	101.5 ± 15.5	103.9 ± 14.3	103.5 ± 20.9	NS	105.3 ± 18.3	107.1 ± 18	102.0 ± 19.3	NS	109.0 ± 4.2	108.4 ± 11.6	102.5 ± 20.1	NS
SAD (cm)	30.3 ± 2.3	31.3 ± 2.2	28.9 ± 2.2	NS	28.1 ± 2.3	29.2 ± 2.3	29.6 ± 2.4	NS	31.2 ± 2.0	32.0 ± 1.8	28.6 ± 2.0	NS
Systolic BP (mm Hg)	117.7 ± 13.9	124.1 ± 13.9*	119.2 ± 15.5†	0.03	122.6 ± 12.3	122.3 ± 16.3	119.9 ± 14.5	NS	126.5 ± 16.3	124.6 ± 15.4	120.3 ± 14.9	NS
Diastolic BP (mm Hg)	77.1 ± 7.9	78.6 ± 9.1	76.8 ± 9.7	NS	79.2 ± 10.2	76.4 ± 9.3	77.8 ± 9.2	NS	78.1 ± 10.3	79.1 ± 10.7	77.3 ± 9.1	NS
T. Cholesterol (mmol/l)	4.5 ± 1.2	4.7 ± 0.91	4.7 ± 1.0	NS	4.6 ± 0.9	4.9 ± 0.9	4.6 ± 1.0	NS	3.1 ± 1.4	4.6 ± 1.0	4.7 ± 1.0	0.006
HDL-C (mmol/l)	0.85 ± 0.3	1.1 ± 0.3*	1.0 ± 0.3*	0.01	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	NS	1.0 ± 0.2	1.0 ± 0.3	1.1 ± 0.3	NS
Triglycerides (mmol/l)	2.1 ± 0.4	1.7 ± 0.3	1.5 ± 0.30*	0.04	1.3 ± 0.6	1.7 ± 0.8	1.7 ± 0.9	NS	1.0 ± 0.40	1.8 ± 0.3	1.7 ± 0.25	NS
LDL-C (mmol/l)	3.1 ± 0.8	3.3 ± 0.8	3.3 ± 0.98	NS	3.2 ± 0.9	3.6 ± 0.8*	3.3 ± 0.9	0.04	3.1 ± 0.9	3.3 ± 1.0*	3.3 ± 0.9*	0.002
Vitamin D (nmol/l)	38.8 ± 1.6	35.1 ± 1.5	33.5 ± 1.7	NS	39.0 ± 1.6	35.6 ± 1.8	34.1 ± 1.6	NS	29.1 ± 1.3	35.1 ± 1.6	34.4 ± 1.7	NS
Ca (mmol/l)	2.2 ± 0.2	2.3 ± 0.2	2.3 ± 0.22	NS	2.2 ± 0.2	2.2 ± 0.2	2.3 ± 0.2†	<0.001	2.3 ± 0.3	2.2 ± 0.2	2.3 ± 0.2*	0.04
Corrected Ca (mmol/l)	2.2 ± 0.3	2.3 ± 0.2	2.3 ± 0.17*	0.01	2.2 ± 0.1	2.3 ± 0.1	2.3 ± 0.2*	0.03	2.4 ± 0.3	2.2 ± 0.1	2.3 ± 0.2	NS
Pi (mmol/l)	1.1 ± 0.3	1.1 ± 0.2	1.2 ± 0.29	NS	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.3	NS	1.1 ± 0.2	1.1 ± 0.3	1.2 ± 0.3	NS
Albumin (g/l)	37.5 ± 7.5	38.8 ± 6.6	38.7 ± 6.2	NS	38.8 ± 6.2	35.8 ± 6.1	39.1 ± 6.4†	0.002	38.8 ± 5.4	37.5 ± 6.9	38.7 ± 6.4	NS

*-indicates significant difference as compared to first group; †-indicates significance as compared to second group.

Table 3. Association between different PTH SNP genotypes and serum vitamin d levels of different nationals

	rs10500784			rs10500783			rs1459015		
	CC + AC	AA	*P*	CT + TT	CC	*P*	TT + CT	CC	*P*
Yemeni	27.4 ± 2.0	30.0 ± 1.8	NS	32.6 ± 1.7	28.6 ± 1.8	NS	30.5 ± 1.8	27.5 ± 1.7	NS
Sudanese	30.7 ± 1.6	31.6 ± 1.7	NS	31.8 ± 1.7	31.9 ± 1.8	NS	36.4 ± 1.8	29.4 ± 1.6	0.03
Indian	34.4 ± 1.7	42.8 ± 2.0	NS	46.7 ± 1.8	40.1 ± 1.6	NS	44.1 ± 2.0	40.6 ± 1.9	NS
Egyptian	40.8 ± 2.1	37.5 ± 1.6	NS	38.3 ± 1.8	38.8 ± 1.6	NS	35.9 ± 1.5	40.2 ± 1.6	NS
Saudi	41.9 ± 2.2	35.3 ± 1.7	NS	45.3 ± 1.8	30.6 ± 1.6	0.03	34.1 ± 1.4	36.1 ± 1.9	NS

Data represented by mean serum vitamin D levels.

mass index (BMI) was 28.1 ± 6.2. The mean serum cholesterol concentration of Saudis was significantly different from that of Egyptians (*P*=0.03). The mean HDL values of Indians, Egyptians and Saudis were significantly different from that of Yemenis, Indians, Sudanese and Egyptians, respectively (*P*<0.001). The mean serum triglycerides levels in Indians and Egyptians were significantly different from that of Yemenis and Indians, respectively (P=0.01). The mean 25(OH)D level of Indians were different from Yemenis and Sudanese and Egyptians were significantly different from that of and Yemenis, respectively (*P*<0.001). The mean serum calcium of Indians was significantly different from that of Yemenis and Sudanese (*P*<0.001). The mean corrected serum calcium in Indians was different from that of Yeminis and Sudanese and that of Egyptians and Saudis was different from that of Indians. Mean serum albumin in Indians and Egyptians was significantly different from that of Yemenis and Sudanese, and Indians, respectively. The percentage of subjects with vitamin D deficiency was high in all the populations and 82.2, 80.4, 59.2, 66.7 and 70.4 percentages of Yemenis, Sudanese, Indian, Egyptian and Saudi, respectively, were deficient in vitamin D. The prevalence of vitamin D deficiency was highest in Yemenis and Sudanese and lowest in Indians.

The means of various anthropometric and biochemical parameters corresponding to different genotypes of PTH SNPs rs1459015, rs10500783 and rs10500784 were compared and the results are presented in **Table 2**. Carriers of AA genotype of SNP rs10500784 were associated with higher level of cholesterol than carriers of CC genotype (*P*=0.006). Carriers of TT genotype of SNP rs1459015 were associated with lower levels of HDL (*P*=0.01) compared to carriers of CC and CT genotypes. Carriers of TT genotype of SNP rs1459015 were associated with higher level of triglycerides compared to carriers of CC genotype (*P*=0.04). Carriers of the heterozygous CT genotype of SNP rs10500783 were associated with significantly higher levels of LDL compared to carriers of TT genotype (*P*=0.04). Carriers of CC genotype of SNP rs10500783 (*P*=0.001) and AA genotype of SNP rs10500784 (*P*=0.002) were associated with higher level of calcium. Carriers of CC genotype of SNP rs10500783 were associated with higher level of corrected calcium (*P*=0.03). Carriers of CC genotype of SNP rs10500783 were associated with higher level of albumin compared to carriers of CT genotypes (*P*=0.002).

Since PTH may play a role in homeostastis of physiological calcium by altering levels of vitamin D, we wanted to see if the different genotypes of PTH, with respect to three SNPs, were associated with differing 25(OH)D levels. For this purpose we genotyped all the subjects for three PTH SNPs and correlated the mean 25(OH)D levels corresponding to different genotypes for each nationality and the results are presented in **Table 3**. The T allele of SNP rs1459015 was associated with higher levels of 25(OH)D in only the Sudanese (P=0.03). The T allele of SNP rs10500783 was associated with higher levels of 25(OH)D only in the Saudi nationals (*P*=0.03).

The different genotypes of the PTH SNPs were analyzed for association with vitamin D deficiency in individual nationals and the results are presented in **Table 4**. Carriers of CC genotype of SNP rs1459015 were associated with higher risk of suffering from vitamin D deficiency (*P*=0.02) and this relation was found only in the Sudanese. Genotypes of other PTH SNPs

Table 4. Association between different PTH SNP genotypes and risk of vitamin d deficiency in different nationals

Serum Vitamin D	rs10500784			rs10500783			rs1459015		
	Reference	Odds ratio (95% CI)		Reference	Odds ratio (95% CI)		Reference	Odds ratio (95% CI)	
	AA	CC + AC	*P*	CC	CT + TT	*P*	CC	TT + CT	*P*
Yemeni	1.0	2.3 (0.26, 6.3)	NS	1.0	0.73 (0.20, 2.6)	0.63	1.0	0.84 (0.27, 2.5)	NS
Sudanese	1.0	1.7 (0.35, 8.2)	NS	1.0	0.62 (0.21, 1.9)	0.40	1.0	0.29 (0.10, 0.83)	0.02
Indian	1.0	2.3 (0.42, 13.0)	NS	1.0	1.2 (0.25, 5.8)	0.81	1.0	0.58 (0.17, 1.9)	NS
Egyptian	1.0	0.51 (0.19, 1.3)	NS	1.0	0.67 (0.24, 1.8)	0.44	1.0	1.6 (0.73, 3.5)	NS
Saudi	1.0	0.87 (0.06, 10.3)	NS	1.0	0.46 (0.08, 2.5)	0.37	1.0	0.97 (0.17, 5.3)	NS

Multinomial logistic regression done for Vitamin D deficiency (<50 nmol/l); *P*-value significant at 0.05.

were not significantly associated with vitamin D deficiency in subjects of any nationality.

Discussion

Heterogeneity observed in the level of 25(OH)D in various populations has been attributed to several important determinants, including exposure to sunlight and dietary level of vitamin D [19]. PTH has a crucial role in regulating the level of 1, 25(OH)2D, the active form of vitamin D, and further, PTH gene SNPs have been related to bone growth and development [20]. Since SNP genotypes are conserved among different ethnic populations, this study was designed to study the effect of different PTH SNP genotypes on serum 25(OH)D concentration by comparing the relation between genotype and vitamin D level of different nationals living in Riyadh. The means of 25(OH)D levels corresponding to different genotypes of PTH SNPs showed that the T allele of SNP rs1459015 was associated with higher level of 25(OH)D in only Sudanese and the T allele of SNP rs10500783 was associated with higher level of 25(OH)D in only Saudi nationals. Analysis of different genotypes of the PTH SNPs for association with vitamin D deficiency in individual nationals showed that Sudanese carriers of CC genotype of SNP rs1459015 had higher risk of suffering from vitamin D deficiency.

Vitamin D deficiency was defined as 25-OH vitamin D levels <50 nmol/l as recommended by the 13th Workshop Consensus for Vitamin D Nutritional Guidelines held in British Columbia, Canada [21]. A large proportion of healthy adults living in Riyadh showed vitamin D deficiency and this is in agreement with an earlier report [22]. Studies carried out in the last two decades indicate a high prevalence of vitamin D deficiency in many other sunlight-rich countries such as Turkey, United Arab Emirates, Kuwait, Bangladesh, Tunisia, Oman and Malaysia [23-26].

Large differences in the incidence of vitamin D deficiency among different nationals might be because of several ethnicity related factors. Previous studies have found significant differences in the 25(OH)D levels between different ethnic groups [27, 28]. Different nationals differ with respect to pigmentation of skin, dietary factors and cultural practices relating to sun exposure. Higher melanin levels in the skin of dark-skinned people block the action of sunlight on vitamin D precursors in the skin, requiring much longer sunlight exposure to generate adequate circulating vitamin D compared to fair skinned people. East Africans, particularly the Sudanese Dinka, have very dark skin which is related to low vitamin D production. Men of African descent required six times more Ultraviolet (UV) irradiation to achieve the same serum 25(OH)D level as Caucasian subjects [29, 30]. This is in agreement with our results showing Indian and Egyptian subjects having higher levels of serum vitamin D than Yemenis and Sudanese nationals. However, Saudis, mostly with fair skin, also had lower levels of 25(OH)D and higher incidence of deficiency indicating that factors other than skin pigmentation, such as the socio-economic status or solar UVB exposure may play a role. Because there are very few food items that are rich in vitamin D [31], the differences in vitamin D status are unlikely to be due to dietary habits.

Ethnicity remained associated with 25(OH)D after adjusting for ITA skin color and skin reaction-to-sun exposure in a New Zealand study involving European, Maori, Pacific and Asian subjects [32] indicating that hereditary factors other than those that determine skin color may contribute to serum vitamin D deficiency. Significant allelic and genotypic differences between Caucasian and Chinese populations were demonstrated for several candidate genes, including PTH, for osteoporosis. PTH SNP association studies in mainly Asian populations have shown positive results with bone mineral density (BMD) [7, 9, 33]. However, all of these studies involved relatively small numbers of individuals. Since PTH level has been directly associated with BMD and osteoporosis, we assessed the association of various genotypes of PTH with serum calcium and corrected calcium levels. Variant of SNP rs10500783 was significantly associated with both calcium and corrected calcium, while variant of SNP rs10500784 was associated with only serum calcium.

Recent studies have also shown an association between low serum 25(OH)D levels and metabolic syndrome characterized by elevated triglycerides and low HDL cholesterol [34]. The mechanism(s) underlying the association between the PTH genotypes of our study and 25(OH)D levels may be due to either altered PTH levels or indirect mechanisms related to expression/function of other genes. Of the three SNPs, only the C allelic variant of SNP rs1459015 was associated with vitamin D deficiency and that too only in the Sudanese nationals. Currently, it is difficult to explain this association due to the relatively distant upstream location of this SNP from the start codon.

The authors acknowledge certain limitations of this study. While we suggest that much of the vitamin D deficiency is attributable to ethnicity, the substantial time spent in KSA may have mitigated this factor and this study would have benefited from further investigation on whether the current results may have been influenced by change of living habits since arriving in KSA. The strength of the associations conferred by each of the genetic variants to altered 25(OH)D levels was small and could have been confounded by unknown variables and this is a common deficiency among such studies. Confirmation of functional outcomes of common variants in the human genome, even if real, needs very large sample sizes to overcome additional genetic and environmental modifiers; however, the limitation resulting from the need for huge sample sizes may be overcome by replication of associations in several independent studies with small sample sizes.

In summary, this study performed on immigrants of several nationalities and natives living in Riyadh, Saudi Arabia, indicated high prevalence of vitamin D deficiency, the extent of which differed between nationalities. Significant associations were found between certain allelic variants of PTH promoter region SNPs and altered 25(OH)D levels in certain nationalities. Replication of these results in larger/independent studies may shed light on the mechanisms underlying ethnicity/nationality associated differences in 25(OH)D levels in humans.

Acknowledgements

The project was financially supported by Vice Deanship of Research Chairs, King Saud University, Riyadh, Saudi Arabia.

Disclosure of conflict of interest

None.

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