



Vitamin D-binding protein and vitamin D receptor genotypes and 25-hydroxyvitamin D levels are associated with development of aortic and mitral valve calcification and coronary artery diseases

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Abstract

To assess the association between vitamin D-Binding Protein (VDBP rs7041T>G) and vitamin D receptor (VDR rs1544410G>A) gene polymorphisms with susceptibility to cardiovascular diseases in population from west of Iran. Two hundred forty-nine individuals with cardiovascular disease (92 with aortic and Mitral Valves Calcification (AMVC) and 157 with Coronary Artery Diseases (CAD) that their diseases were confirmed by echocardiography and angiography and unrelated 182 healthy controls (gender and age-matched) were selected for this case–control study. The VDR rs1544410G>A, and VDBP rs7041T>G genotyping were detected by PCR–RFLP, serum vitamin D and lipid concentrations were measured by ELISA and enzyme assay, respectively. The VDR rs1544410G>A gene is a strong risk factor for CAD (OR = 1.28, p = 0.002) and the dominant genotype (T/G+G/G) of VDBP rs7041 T>G SNP plays a protective role (OR = 0.67, p = 0.003) in AMVC development in studied population. In addition, lower level of vitamin D strongly increased the risk of CAD (15 ± 11.02 vs. 21.3 ± 18 µg/L, p = 0.043) and AMVC (12.1 ± 13.1 vs. 21.3 ± 18 µg/L, p = 0.014) development in individuals carrying T/T genotype of VDBP rs7041 T>G gene polymorphism. There was a strong interaction between A allele VDR rs1544410 and G allele of VDBP rs7041 genes in a protective role (OR = 0.74, p = 0.044) in AMVC patients). CAD and AMVC patients were deficient in vitamin D, i.e. their level of vitamin D was strongly lower than that in the control group. Our findings for the first time indicated that there is a strong association between vitamin D deficiency, lipid profile and the VDR rs1544410G>A and rs7041T>G VDBP genes polymorphisms. These interactions may be one of the important factors for CAD and AMVC incidence.

Keywords Vitamin D receptor (VDR) gene · Vitamin D-binding protein (VDBP) gene · Coronary artery disease (CAD) · Aortic and mitral valves calcification (AMVC) · Vitamin D

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Introduction

Cardiovascular diseases (CVDs) is the first cause of death worldwide [1, 2]. Calcification of the aortic valve or mitral annulus and CAD are major causes of CVD in elderly [3]. Although CAD has a complex etiopathogenesis and a multifactorial origin, it is most commonly caused by atherosclerosis [4]. Although the exact molecular mechanism leading to CVD is unclear, cigarette smoking, hypertension, hyperlipidemia, genetic predisposition, lack of physical activity, obesity and vitamin D (Vit D) deficiency may be a risk factor for incidence of CVD [5, 6].

Vitamin D not only regulates calcium and phosphorous homeostasis, however it also plays important role in physiological functions [6]. Over the past decade, evidences suggested that there was a positive association between low vitamin D level and CVD susceptibility or mortality [6, 7]. Norman et al. reported that although vitamin D is essential for cardiovascular health, its excess could have unintended health consequence, including elastolysis induced by inflammatory processes [8]. In females, vitamin D deficiency is associated with the severity of CAD, but in males, vitamin D status is independently related to CAD susceptibility [9].

The main transport protein of vitamin D in the plasma is vitamin D-binding protein (VDBP) with a molecular weight of (58 kDa). The amount of active vitamin D in the bloodstream depends strongly on the VDBP concentration [10]. The VDBP/25-hydroxy vitamin D [25(OH)D] complex formation, its filtration, and reabsorption through vitamin D receptors (VDRs) in renal tubular cells are important factors in providing optimal levels of Vit D in circulation [11].

Previous studies reported that single nucleotide polymorphisms (SNPs) of rs1544410 and rs7041 in VDR and VDBP genes, respectively are potential risk factors for CAD and vascular calcification [8, 12, 13]. The SNPs in the VDR and VDBP genes lead to production of variant proteins with different affinity for vitamin D [13]. The VDBP gene has located on the chromosome 4 and the SNP of rs7041 in exon11 of this gene is significantly associated with low circulating 25(OH)D concentration in different populations [14, 15]. VDR gene is located on chromosome 12 and the rs1544410>A BsmI (rs1544410) SNP is located at the 3' end of the gene [16]. VDR rs1544410G>A SNP does not change the amino acid sequence of the VDR protein, however, it may affect on alteration of mRNA stability and consequently gene expression, also it might change the splicing sites or alter the intronic regulatory elements [16]. The best of our knowledge, the association of VDR rs1544410G>A and VDBP rs7041T>G SNPs with susceptibility to AMVC

and CAD has not been studied. Here, the role of VDR rs1544410G>A and VDBP rs7041T>G SNPs in susceptibility to CAD and AMVC and their effects on systolic and diastolic pressure, vitamin D, Ca, phosphate and lipid profile concentrations in circulation in population from west of Iran were studied. In this study, we found for the first time, that there is a strong association between vitamin D deficiency, lipid profile and the VDR rs1544410G>A and rs7041T>G VDBP genes polymorphisms. These interactions may be one of the important factors for CAD and AMVC incidence.

Materials and methods

Ethics Committee of Kermanshah University of Medical Sciences, Iran approved this study according to the principles of the Declaration of Helsinki I. All participants were signed a written informed consent.

Subjects

A total of 249 patients (92 with AMVC and 157 with CAD, mean age, 64.6 ± 9.8 years; range, 40–88 years) were recruited from Imam Ali hospital. The MVC and AVC were diagnosed according to Doppler echocardiography. The criteria for detection of aorta stenosis in mild AVC was the aortic jet velocity 2.5–2.9 (m/s), mean gradient < 25 mmHg and the aortic valve area of 1.5–2 cm², for moderate AVC the criteria were the aortic jet velocity 3–4 (m/s), mean gradient 25–49 mmHg and the aortic valve area of 1–1.5 cm². The criteria for detection of severe AVC were the aortic jet velocity > 4 (m/s), mean gradient > 40 mmHg and the area of aortic valve of < 1 cm².

The criteria for mild MVC was the pulmonary artery pressure < 30 mmHg and mean gradient < 5 mmHg and Mitral valve area > 1.5 cm², for moderate MVC the criteria were the pulmonary artery pressure 30–40 mmHg and mean gradient 5–10 mmHg and Mitral valve area < 1 cm².

The CAD was diagnosed by having a greater than 50% diameter stenosis of one or more major coronary vessel as detected by angiography.

The systolic (SBP) and diastolic (DBP) blood pressures and body mass index (BMI) of each individual were measured.

The healthy control volunteers (182, mean age, 63.7 ± 7.2 years; range 47–81 years) were recruited from subjects that were referred to the blood bank of Kermanshah province. The selected individuals were those without CVD and also with the absence of specific diseases (heart and vascular, liver, kidney, diabetes mellitus and major diseases) at their annual medical checkup.

Chemical analyses

Serum lipid profiles included LDL-C, HDL-C, triglyceride (TG), and the serum levels of Ca (mg/dL), Phosphate (mg/dL), urea, creatinine, and fasting blood sugar (FBS) (mg/dL) were determined by the enzymatic method (Pars Azmon kit, Iran), using an automated Erba XL- 600 (Mannheim, Germany).

Serum vitamin D ($\mu\text{g/L}$) concentration was determined by ELISA according to the manufacturer's instructions (Monobind Ink Kit, USA).

DNA extraction, VDR 63980G>A, and VDBP 7904T>G genotyping

Phenol chloroform method was used for extracting the genomic DNA from EDTA treated blood samples [17]. The VDR rs1544410G>A and VDBP rs7041T>G genes polymorphisms were determined by PCR–RFLP technique.

The forward 5'-CAACCAAGACTACAAGTACCGCGTCAGTGA-3' and reverse 5'-AACCAGCGGAAGAGGTC AAGGG-3' primers were used to identify VDR rs1544410G>A gene polymorphism. The 25 μl PCR reaction mixtures were containing 50–100 ng DNA, primers, and dNTPs. Denaturation of DNA at 95 °C for 5 min was followed by 35 cycles of 95 °C for 1 min, 65.7 °C for 1 min and 72 °C for 1 min. A temperature of 72 °C for 10 min was used as final extension. The size of PCR products was 822 bp [18].

The BsmI restriction endonuclease was used for digestion of PCR products at 37 °C overnight and the digested PCR products were detected by electrophoresis using a 2 percent agarose gel contained ethidium bromide and photographed under UV transilluminator. The length of digested fragments for homozygote mutant AA was 822 bp, for heterozygote mutant GA were 822 bp, 645 bp, and 177 bp and for homozygote wild GG was 645 bp and 177 bp as shown in Fig. 1.

The forward 5'-AAATAATGAGCAAATGAAAGAAGAC-3' and reverse 5'-CAATAACAGGAAAGAAATGAGTAGA-3' primers were used to identify VDBP rs7041T>G polymorphism. In brief, the PCR reaction consisted of DNA denaturation at 94 °C for 5 min, followed by 35 cycles at 94 °C for 30 s, 51 °C for 30 secs, and 72 °C for 45 secs, with a final extension at 72 °C for 10 min. After amplification, the PCR products (483 bp) were digested with the HaeIII restriction enzyme. Wild type TT genotype showed a 483 bp product, whereas homozygous mutant GG genotype showed two fragments (298 and 185 bp) and heterozygous TG genotype showed three fragments (483, 298, and 185 bp) (Fig. 2) [19].

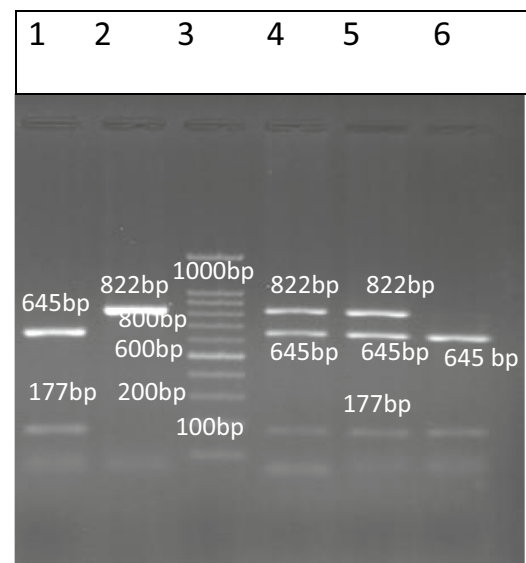


Fig. 1 A 2% agarose gel electrophoresis patterns for VDR rs1544410G>A gene polymorphism alleles analyzed by PCR–RFLP. Lane 1 and 6, are homozygous wild-type (G/G), Lane 2 undigested PCR product; Lanes 3 and 7, homozygous mutant, Lane 4, 100 bp DNA ladder; Lanes 5, heterozygous mutant (A/G)

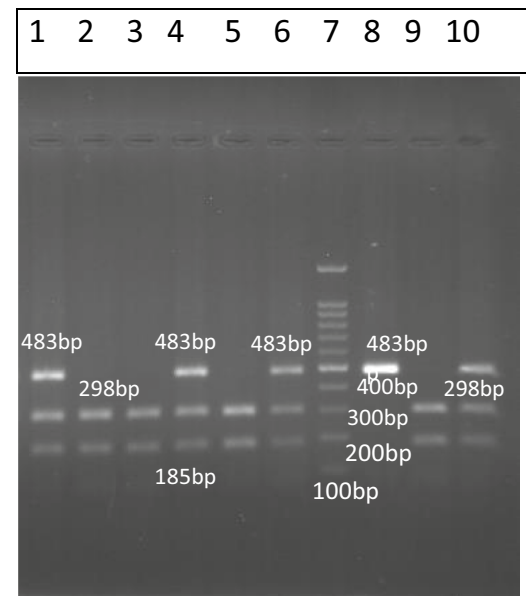


Fig. 2 A 2% agarose gel electrophoresis patterns for VDBP rs7041T>G gene polymorphism alleles analyzed by PCR–RFLP. Lane 1, 4 and 10, are heterozygous -type (G/T); Lane 2, 3 and 5 homozygous wild type(G/G); Lane 7, 100 bp DNA ladder; Lane 9, undigested PCR product; Lanes 3 and 7, homozygous mutant; Lanes 5, heterozygous mutant (T/T)

Validation of the methods by Sanger sequencing

The presence of VDR rs1544410G>A and VDBP rs7041T>G genes mutations were confirmed by genomic DNA sequencing. To verify the obtained genotypes, Sanger sequencing was also employed as our reference method. For this purpose, some samples from each genotype were subjected to sequencing. The results of Sanger sequencing were determined by Chromas program (Technelysium Pty. Ltd, Helensvale, Queensland, Australia).

Statistical analyses

The χ^2 test was used to compared the frequencies of VDR rs1544410G>A and VDBP rs70414T>G in patients with calcification of the aortic and mitral valves and also in CAD patients. The Hardy–Weinberg equilibrium for analyzing the agreement of the frequencies of observed genotype with those expected genotypes was approved using χ^2 test. The relative risk of the disease was calculated by Odds ratios (OR) and 95% confidence intervals (CI) was obtained by SPSS logistic regression. The correlation values of serum LDL-C, HDL-C, TG, vitamin D, Ca, Phosphate, FBS, urea, creatinine, MI, age, systolic and diastolic pressures between three groups were calculated using linear regression and an unpaired *t* test. The quantitative data were compared using *t*-test, ANOVA and nonparametric independent sample Mann–Whitney analysis. For analyzing the data, the SPSS 16 Software was used. The P value < 0.05 considered as statistical significance.

Results

The results of laboratory tests and demographic characteristics of patients and control group are depicted in Table 1. Comparing CAD and AMCV patients with controls indicated strongly lower serum concentrations of vitamin D (13.5 (7.7–21.2, *p*=0.02) and 8.9 (8.6–14.6, *p*=0.025) versus 16.2 (5.2–26.2), HDL-C (41 (35–45, *p*<0.001) and 44 (39.2–50, *p*=0.001 vs. 50 (43–60)), and Ca (9.2 (8.3–9.9, *p*<0.001) and 9.2 (8.3–9.9, *p*<0.001) vs. 9.4 (8.7–10.1)) and higher levels of LDL-C (95.1 ± 32.9, *p*=0.005) and 89.3 (61.3–117.7, *p*=0.04) vs. 86 (63.3–110) FBS (100 (90–114.5), *p*<0.001 and 98.8 (90–106, *p*=0.002) vs. 93 (87.7–99), creatinine (1.14 ± 2.9 vs. 0.8 ± 0.14, *p*<0.001), urea 40 (32–50, *p*<0.001) and 34 (29.2–39.7, *p*<0.001) vs. 29(25–32), respectively (Table 1).

In addition, the values of systolic and diastolic blood pressures were strongly higher in CAD and AMCV patients than control group, *p*<0.001 (Table 1).

The frequencies of VDR rs1544410G>A and VDBP rs7041T>G genotypes and alleles in CAD and AMVC patients and controls are demonstrated in Table 2. Also, the frequency of VDR rs1544410G>A and VDBP rs7041T>G alleles in CAD and AMVC patients and controls as well as vitamin D level distributions are demonstrated in Figs. 3 and 4, respectively.

The overall distribution of VDR 63980G>A genotypes ($\chi^2=8.9$, *df*=2, *p*=0.011) and alleles ($\chi^2.9$, *df*=1, *p*=0.002) in CAD patients were strongly different compared to controls (Table 2). The presence of dominant (G/A + A/A vs. G/G) genotypes [1.34 (1.05–1.7, *p*=0.015)]

Table 1 Comparison levels of vitamin D, lipid profiles, biochemical variables and other demographic characteristics among CAD, AMVC patients and control group

Variable	CAD	AMVC	Control
Age (year)	63.4 ± 8.8 <i>p</i> =0.5	63.5 ± 9.7 <i>p</i> =0.6	64.09 ± 7.5
BMI (kg/m ²)	24.9 ± 2.9 <i>p</i> =0.06	24.6 ± 2.9 <i>p</i> =0.5	24.4 ± 2.5
Vitamin D (µg/L)	13.5 (7.75–21.2) <i>p</i> =0.02	8.9 (8.6–14.6) <i>p</i> =0.025	16.2 (5.2–26.2)
Cholesterol (mg/dL)	160 (131–199) <i>p</i> =0.2	150 (123.7–188.5) <i>p</i> =0.05	160 (137–186)
Triglyceride (mg/dL)	112 ± 51.6 <i>p</i> =0.07	122 ± 43.7 <i>p</i> =0.7	121 ± 28.8
LDL-C (mg/dL)	95.1 ± 32.9 <i>p</i> =0.005	89.3 (61.3–117.7) <i>p</i> =0.04	86 (63.3–110)
HDL-C (mg/dL)	41 (35–45) <i>p</i> <0.001	44 (39.2–50) <i>p</i> =0.001	50 (43–60)
Ca (mg/dL)	9.2 (8.3–9.9) <i>p</i> <0.001	8.5 (7.8–9.3) <i>p</i> <0.001	9.4 (8.7–10.1)
Phosphate (mg/dL)	4.3 (3.9–4.5) <i>p</i> =0.3	4.5 (4.2–4.8) <i>p</i> =0.033	4.4 (4.1–4.5)
Fasting blood sugar (mg/dL)	100 (90–114.5) <i>p</i> <0.001	98.5 (90–106) <i>p</i> =0.002	93 (87.7–99)
Urea (mg/dL)	40 (32–50) <i>p</i> <0.001	34 (29.2–39.7) <i>p</i> <0.001	29 (25–32)
Creatinine (mg/dL)	1.14 ± 2.9 <i>p</i> <0.001	0.9 ± 0.15 <i>p</i> =0.2	0.8 ± 0.14
Systole pressure (mmHg)	131 (123–142) <i>p</i> <0.001	124 (112–140) <i>p</i> <0.001	110 (101–116)
Diastole pressure (mmHg)	84 (78–90) <i>p</i> <0.001	80 (75–90) <i>p</i> <0.001	75 (66–76)

Statistical analyses were done using *t*-test and by non-parametric two independent samples test Mann–Whitney

Table 2 Odd ratio and distribution of VDBP rs7041T>G) and VDR (rs1544410) G>A Bsm1 genotypes and alleles between CAD and AMVC with control group

VDR rs1544410 G>A genotypes	CAD (n= 157)	Control (n= 182)	AMVC (n=92)
G/G	40 (25.5%)	69 (37.9%)	36 (39.1%)
G/A	69 (43.9%)	79 (43.4%)	41 (44.6%)
A/A	48 (30.6%)	34 (18.6%)	15 (16.3%)
	($\chi^2=8.9$, df=2, p=0.011)		($\chi^2=.22$, df=2, p=0.89)
	OR (95% confidential)		OR (95% confidential)
Dominant G/A+A/A vs. G/G	1.34 (1.05–1.7, p=0.015) (n= 117 vs. n=40)	(n= 113 vs. n=69)	0.97 (0.74–1.3, p=0.3) (n=56 vs. n=36)
VDR 1544410G>A alleles	CAD vs. Control OR (95% confidential interval)	Control	AMVC (n= 81) OR (95% confidential interval)
G	n= 149	n= 217	n= 113
A	1.28 (1.09–1.5, p=0.002, n= 165)	n= 147	0.96 (0.7–1.1, p=0.6, n= 71)
	($\chi^2=9.9$, df=1, p=0.002)		($\chi^2=0.16$, df=1, p=0.6)
VDBP rs7041 genotypes	CAD (n=89)	Control (n= 182)	AMVC (n=92)
T/T	42 (26.8%)	48 (26.4%)	41 (44.8%)
T/G	83 (52.5%)	81 (44.5%)	43 (46.7%)
G/G	32 (20.4%)	53(29.1%)	8 (8.7%)
	($\chi^2=3.8$, df=2, p=0.15)		($\chi^2=17.7$, df=2, p<0.001)
	OR (95% confidential interval)	Control	AMCV
Dominant T/G+G/G vs. T/T	0.9 (0.79–1.26, p=0.93) (n= 115 vs. n=42)	(n= 134 vs. n=48)	0.67 (0.51–0.87, p=0.003) (n=51 vs. n=41)
VDBP T/G alleles	CAD vs. Control OR (95% confidential interval)	Control	AMCV OR (95% confidential interval)
T	n= 167	n= 177	n= 125
G	0.91 (0.8–1.06, p=0.2, n= 147)	n= 187	0.66 (0.5–0.8, p ≥ 0.001)
	($\chi^2=1.4$, df=1, p=0.2)		($\chi^2=18.4$, df=1, p<0.001)

and the A allele [1.28 (1.09–1.5, p=0.002, n= 165)] of VDR rs1544410G>A SNP strongly increased the risk of CAD in the population studied. Interestingly, a strong difference was found between VDBP rs7041T>G) genotypes ($\chi^2=17.7$, df=2, p<0.001) and alleles ($\chi^2=8.4$, df=1, p<0.001) frequencies in patients with AMVC and control group (Table 2). Dominant (T/G + G/G) genotype of VDBP rs7041T>G SNP had a trend to decrease the risk of AMVC disease [0.67 (0.51–0.87, p=0.003)]. The VDBP rs7041T>G genotype and allele frequencies in patients with CAD were similar to the control group (Table 2).

We analyzed the association of GG and GA+AA genotypes of VDR rs1544410 (Table 3), TT and TG+GG genotypes of VDBP rs7041 (Table 4) with serum levels of vitamin D, LDL-C, HDL-C, TC, TG, BMI, Ca, phosphate, FBS, urea, and creatinine, as well as with systolic and diastolic blood pressures in CAD and AMVC patients. As shown in the Table 3, we found that CAD patients with dominant

(A/A+A/G) genotype of the VDR rs1544410G>A or with dominant genotype (G/G+G/T vs. TT) of VDBP rs7041T>G SNP had strongly lower levels of HDL-C (40.4 ± 8.1 vs. 51.7 ± 11.8 l p<0.001 and 39.8 ± 8.04 vs. 52.08 ± 12.7, p<0.001, respectively) and Ca (9 ± 1.4 vs. 9.4 ± 0.99, p=0.009 and 8.8 ± 1.5 vs. 9.3 ± 1.1, p=0.01, respectively) compared to controls.

Both VDR rs1544410 (A/A+A/G) and VDBP rs7041(G/G+G/T) in dominant genetic model strongly increased CAD patients' systolic and diastolic blood pressures and serum levels of FBS, urea and creatinine.

A strongly lower level of Vit D (15 ± 11.02 vs. 21.3 ± 18, p=0.043) was detected in CAD patients with TT genotype of VDBP at position 7904 compared to control group (Table 3). Interestingly, in controls there was significantly higher level of HDL-C than the patients with CAD who carrying GG genotype of VDR rs1544410G>A (41.5 ± 7.7 vs. 53.1 ± 11.4, p<0.001) and TT genotype of VDBP

Fig. 3 Allele frequencies of VDR and VDBP have demonstrated in cases and controls in bar charts

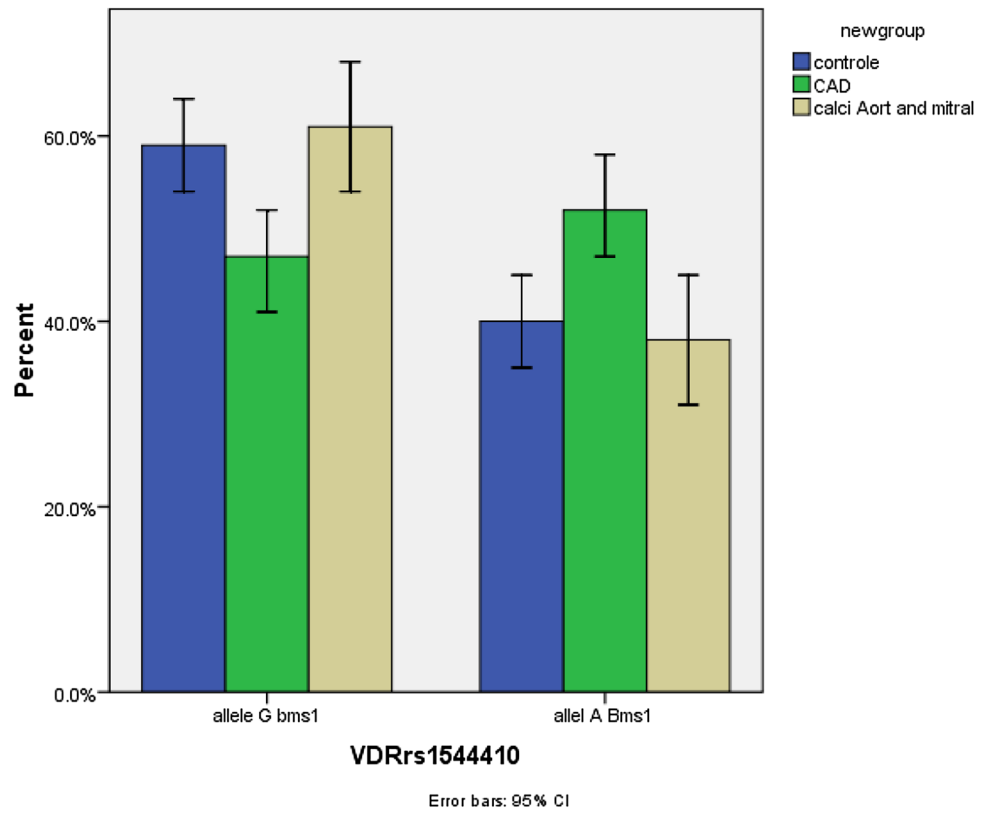


Fig. 4 Vitamin D distributions among in CAD and AMVC patients and controls is demonstrated in Fig. 4

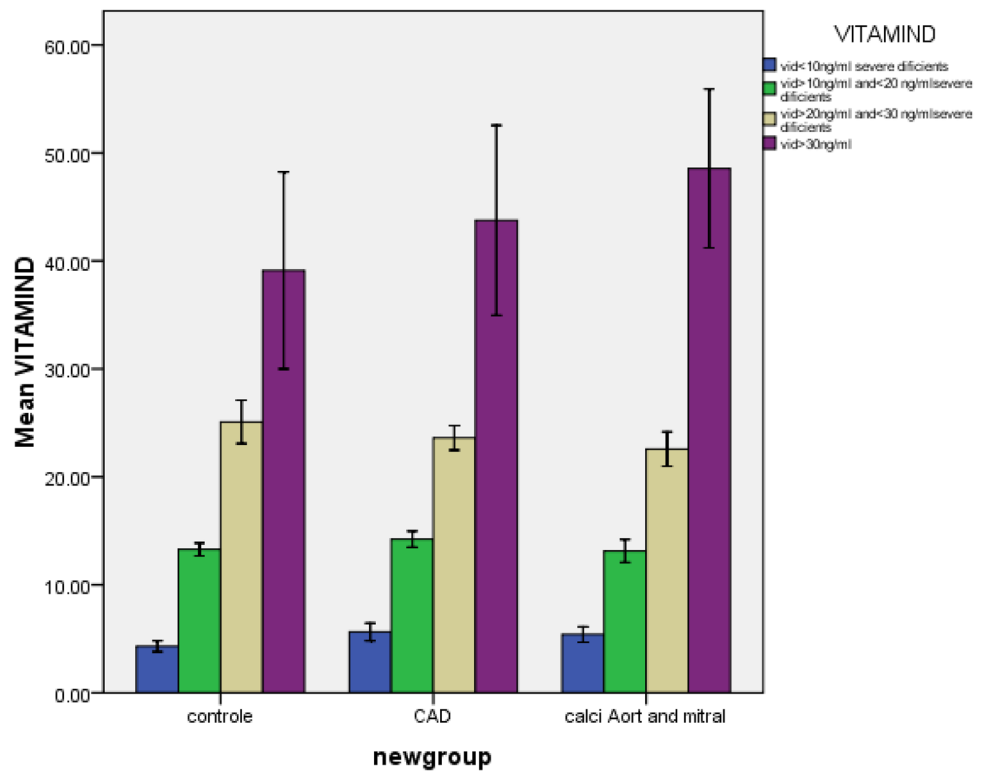


Table 3 Comparison of Vitamin D, LDL-C, HDL-C, TC, TG, Ca, phosphate, FBS, urea, creatinine serum levels and systolic and diastolic blood pressures between VDR rs1544410G>A dominant model (A/A+A/G vs. G/G) and VDBP rs7041T>G dominant model (G/G+G/T vs. T/T) in CAD patients with control subjects

	CAD patients		Control	CAD patients		Control
	VDR rs1544410G>A G/G genotype			VDBP rs7041T>G (rs7041) T/T genotype		
Vit D ($\mu\text{g/L}$)	17.8 \pm 13	(p=0.86)	19.1 \pm 15.2	15 \pm 11.02	(p=0.043)	21.3 \pm 18
Cholesterol (mg/dL)	169.07 \pm 45.1	(p=0.3)	161.9 \pm 31.3	165.2 \pm 4	(p=0.5)	160.5 \pm 29.4
Triglyceride (mg/dL)	129.2 \pm 58.4	(p=0.6)	125.7 \pm 34.7	125.2 \pm 39.2	(p=0.9)	124.7 \pm 22.08
LDL-C (mg/dL)	93.8 \pm 34.6	(p=0.2)	58.1 \pm 30.5	91.04 \pm 30.8	(p=0.2)	84.2 \pm 28.8
HDL-C (mg/dL)	40.05 \pm 7.4	(p<0.001)	52.07 \pm 12.5	41.5 \pm 7.7	(p \leq 0.001)	53.1 \pm 11.4
Systole pressure (mmHg)	134.8 \pm 13.1	(p<0.001)	106.8 \pm 7.5	134.8 \pm 13.1	(p \leq 0.001)	107.5 \pm 8.7
Diastole pressure (mmHg)	83.6 \pm 9.5	(p<0.001)	71.3 \pm 5.8	85.2 \pm 7.4	(p \leq 0.001)	71.3 \pm 5.5
Ca (mg/dL)	9.1 \pm 1.2	(p=0.7)	9.2 \pm 1.2	9.4 \pm 0.97	(p=0.4)	9.2 \pm 0.93
Phosphate (mg/dL)	4.3 \pm 0.6	(p=0.8)	4.3 \pm 0.28	4.3 \pm 0.3	(p=0.7)	64.3 \pm 0.38
FBS (mg/dL)	109.7 \pm 32.6	(p<0.02)	95.5 \pm 15.4	108.7 \pm 31.4	(p \leq 0.001)	91.3 \pm 8.2
Urea (mg/dL)	43.4 \pm 14.9	(p<0.001)	30.2 \pm 5.9	43.4 \pm 12.5	(p \leq 0.001)	27.7 \pm 6.7
Creatinine (mg/dL)	1.1 \pm 0.2	(p<0.001)	0.8 \pm 0.1	1.1 \pm 0.2	(p \leq 0.001)	0.8 \pm 0.1
	Dominant model (A/A+A/G vs. G/G)			Dominant model (G/G+G/T)		
Vit D ($\mu\text{g/L}$)	16 \pm 14.5	(p=0.16)	19.1 \pm 9.19	17 \pm 15.1	(p=0.4)	18.8 \pm 16.2
Cholesterol (mg/dL)	167.1 \pm 43.6	(p=0.1)	160.4 \pm 29.4	168.5 \pm 44.5	(p=0.09)	160.4 \pm 29.7
Triglyceride (mg/dL)	119.5 \pm 40.1	(p=0.9)	119 \pm 25.2	120.8 \pm 47.7	(p=0.8)	119.7 \pm 30.8
LDL-C (mg/dL)	95.6 \pm 32.4	(p=0.05)	87.8 \pm 27.2	96.6 \pm 33.6	(p=0.009)	86.2 \pm 28.5
HDL-C (mg/dL)	40.4 \pm 8.1	(p<0.001)	51.7 \pm 11.8	39.8 \pm 8.04	(p \leq 0.001)	52.08 \pm 12.7
Systole pressure (mmHg)	132.7 \pm 13.09	(p<0.001)	109.1 \pm 8.7	132.4 \pm 13.1	(p \leq 0.001)	108.7 \pm 8.02
Diastole pressure (mmHg)	90.03 \pm 7.4	(p<0.004)	71.5 \pm 5.3	89.5 \pm 66.2	(p=0.002)	71.4 \pm 5.5
Ca (mg/dL)	9 \pm 1.4	(p=0.009)	9.4 \pm 0.99	8.8 \pm 1.5	(p=0.01)	9.3 \pm 1.1
Phosphate (mg/dL)	4.2 \pm 0.5	(p=0.9)	4.3 \pm 0.5	4.2 \pm 0.6	(p=0.5)	4.3 \pm 0.4
FBS (mg/dL)	106.4 \pm 30.4	(p<0.001)	92.5 \pm 9	106.8 \pm 30.7	(p \leq 0.001)	94.3 \pm 10.3
Urea (mg/dL)	43.2 \pm 15.4	(p<0.001)	28.4 \pm 6.03	43.3 \pm 16.05	(p \leq 0.001)	29.2 \pm 5.7
Creatinine (mg/dL)	1.1 \pm 0.23	(p<0.001)	0.9 \pm 0.1	1.1 \pm 0.22	(p \leq 0.001)	0.9 \pm 0.1

rs1544410T>G (40.05 \pm 7.4 vs. 52.07 \pm 12.5, p<0.001) (Table 3).

The CAD patients with GG genotype of VDR rs1544410G>A and TT genotype of VDBP rs7041T>G had strongly higher concentrations of FBS, Creatinine and urea as well as higher systolic and diastolic blood pressures compared with control subjects (Table 3).

In this study we also found that patients with AMVC disease who carry the (A/A+A/G) genotype of VDR 63980G>A SNP (dominant genetic model), the (G/G+G/T) genotype of VDBP rs7041T>G SNP in dominant genetic model had strongly lower concentrations of vitamin D and HDL-C than control subjects (Table 4). In addition, AMVC patients with GG genotype of VDR rs1544410G>A or with one or more copy of A allele of VDR at position 63980 had strongly higher concentrations of LDL-C, phosphate, FBS and urea compared to healthy control group (Table 4).

We analyzed the CAD patients in two groups; group 1 patients were those with one vessel stenosis, group 2 were

those with two or more vessel stenosis. Patients with AMVC disease were also divided into groups based on involvement of aortic and/or mitral valve calcifications (i.e. 1. aortic or mitral valve calcification 2. aortic and mitral valve calcification). Then, we investigated the distribution and OR for the presence of the VDR rs1544410G>A and VDBP rs7041T>G genotypes in each group according to dominant genetic model and reported the results in Table 5. We found that the overall distribution and OR of VDR rs1544410G>A and VDBP rs7041T>G genotypes in 4 groups of patients were similar (Table 5).

The logistic regression analysis was used to investigate the interaction between A allele of VDR rs1544410G>A and G allele of VDBP rs7041T>G in control group, CAD and AMVC patients and the results are demonstrated in Table 6. A strongly association between VDR rs1544410 A and VDBP rs7041, G alleles was observed in AMVC patients ($\chi^2=9.2$, df=3, p=0.027). As depicted in Table 6, the concomitant presence of the G allele of

Table 4 Comparison of Vitamin D, LDL-C, HDL-C, TC, TG, Ca, phosphate, FBS, urea, creatinine serum levels and systolic and diastolic blood pressures between VDBP rs1544410T>G (rs7041) dominant model (G/G+G/T vs. T/T) and VDR 63980G>A G/G vs. A/A+G genotype in AMVC patients with control subjects

	AMVC patients	p Value	Control	AMVC patients	p Value	Control
	VDR rs1544410G>A G/G genotype			VDBP rs1544410T>G (rs7041) T/T genotype		
Vit D (µg/L)	13.1 ± 13.6	p=0.048	19.1 ± 15.2	12.1 ± 13.1	p=0.014	21.3 ± 18
Cholesterol (mg/dL)	169.1 ± 49.3	p=0.3	24.3 ± 2.8	151.2 ± 49.9	p=0.2	160.5 ± 29.4
Triglyceride (mg/dL)	129.5 ± 50.2	p=0.6	161.9 ± 31.3	116.5 ± 40.6	p=0.2	124.7 ± 22.08
LDL-C(mg/dL)	106.4 ± 52.8	p=0.01	125.07 ± 34.7	91.1 ± 54.7	p=0.4	84.2 ± 28.8
HDL-C (mg/dL)	42.2 ± 5.6	p<0.001	55.1 ± 6.5	44.7 ± 8.1	p<0.001	53.1 ± 11.4
Systole pressure (mmHg)	124.9 ± 16.1	p<0.001	106.8 ± 7.5	128.8 ± 19.6	p ≤ 0.001	107.5 ± 8.7
Diastole pressure (mmHg)	83.6 ± 9.5	p<0.001	71.2 ± 5.8	82.02 ± 11.7	p ≤ 0.001	71.3 ± 5.5
Ca (mg/dL)	8.2 ± 0.9	p ≤ 0.001	9.2 ± 1.2	8.5 ± 1.05	p=0.001	9.2 ± 1.2
Phosphate (mg/dL)	4.5 ± 0.56	p=0.03	4.3 ± 0.28	4.4 ± 0.51	p=0.2	4.3 ± 0.38
FBS (mg/dL)	105.3 ± 19.4	p=0.003	95.5 ± 11.5	99.6 ± 15.4	p=0.002	91.3 ± 8.2
Urea (mg/dL)	35.1 ± 7.02	p=0.001	30.2 ± 5.9	33.6 ± 7.7	p ≤ 0.001	27.7 ± 6.7
Creatinine (mg/dL)	0.94 ± 0.17	p=0.08	0.8 ± 0.1	0.93 ± 0.14	p=0.1	0.8 ± 0.1
	Dominant model (A/A+A/G)			Dominant model G/G+G/T)		
Vit D (µg/L)	13.1 ± 14.5	p=0.034	19.1 ± 18.2	13.9 ± 19.8	p=0.047	18.8 ± 16.2
Cholesterol (mg/dL)	153.7 ± 38.9	p=0.2	160.4 ± 29.4	169.4 ± 38.4	p=0.09	160.4 ± 29.7
Triglyceride (mg/dL)	116.3 ± 38.1	p=0.6	119 ± 25.2	126.8 ± 45.9	p=0.2	119.7 ± 30.8
LDL-C(mg/dL)	86.6 ± 36.4	p=0.8	87.8 ± 27.2	98.5 ± 33.9	p=0.01	86.2 ± 28.5
HDL-C (mg/dL)	45.3 ± 8.5	p=0.001	51.7 ± 11.8	44.1 ± 7.6	p ≤ 0.001	52.08 ± 12.7
Systole pressure (mmHg)	124.7 ± 21.3	p ≤ 0.001	109.1 ± 8.7	122.01 ± 18.1	p ≤ 0.001	108.7 ± 8.02
Diastole pressure (mmHg)	81.8 ± 10.06	p ≤ 0.001	71.5 ± 5.3	80.5 ± 8.8	p ≤ 0.001	71.4 ± 5.5
Ca (mg/dL)	8.8 ± 0.9	p ≤ 0.001	9.4 ± 0.99	8.6 ± 0.9	p ≤ 0.001	9.3 ± 1.1
Phosphate (mg/dL)	4.5 ± 0.5	p=0.005	4.3 ± 0.5	4.6 ± 0.4	p ≤ 0.001	4.3 ± 0.4
FBS (mg/dL)	97.4 ± 13.6	p=0.009	92.5 ± 9	101.4 ± 10.3	p=0.001	94.3 ± 10.3
Urea (mg/dL)	32.8 ± 6.9	p ≤ 0.001	28.4 ± 6.03	33.4 ± 7.1	p ≤ 0.001	29.2 ± 5.7
Creatinine (mg/dL)	0.9 ± 0.12	p=0.9	0.9 ± 0.1	0.9 ± 0.16	P=0.7	0.9 ± 0.1

VDBP rs7041 and the A allele of VDR rs1544410 strongly decreased the risk of AMVC disease by 0.74 (0.58–1, $p=0.044$) times.

We also divided the CAD, AMVC patient and control groups based on vitamin D deficiency into 4 groups as shown in Table 7. The distribution of all 4 groups, severe deficiency (< 10 ng/mL), deficient 10 < and < 20 ng/mL, insufficient 20 < and < 30 and sufficient individuals with > 30 ng/mL of Vit D [20].

Deficiency of vitamin D in CAD ($\chi^2=10.5$, $df=3$, $p=0.01$) and AMVC patients ($\chi^2=3.9$, $df=3$, $p=0.003$) was strongly higher than controls. In addition, the frequency of severe deficiency (< 10 ng/mL) of Vit D in AMVC patients (55.4%) was higher compared to CAD patients (35%, $p=0.01$). Vitamin D distribution among CAD and AMVC patients and controls is demonstrated in Fig. 4.

Discussion

Coronary artery disease in conjunction with AMVC are leading cause of death especially in the elderly [21, 22]. These disorders happen as a result of interaction between genetic predisposition and environmental factors [22]. One meta analysis about a comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease reported that 2213 variants (7.6% in dels) have a strong correlation ($p < 5 \times 10^{-8}$) with CAD with a low false discovery rate (FDR q -value $< 2.1 \times 10^{-4}$) [23]. Although our results demonstrated that vitamin D deficiency had the strong genetic association with increased the risk of CAD and AMVC development in our studied population, Manousaki et al. failed to show such an association [24]. These findings suggested that although the

Table 5 The distribution and odds ratio (OR) of VDR rs1544410G>A and VDBP rs7041T>G genotypes according to dominant model between CAD and AMVC patients

Genotypes	CAD patients One vesselstenosis	CAD patients Two or three vessel stenosis
VDBP rs7041T>G)		
T/T	33 (25%)	9 (36%)
G/G+G/T	99 (75%)	16 (64%)
	$\chi^2=1.29, d=1, p=0.2$ 0.9 (0.5–1.4, p=0.7)	
VDR rs1544410 BSM1		
G/G	33 (25%)	7 (28%)
A/A+A/G	99 (75%)	18 (72%)
	$\chi^2=0.1, d=1, p=0.7$ 0.9 (0.5–1.4, p=0.7)	
Genotypes	AMVC patients Aorta or mitral valve calcified	AMVC patients Aorta and mitral valves calcified
VDBP7041T>G)		
T/T	37 (46.3%)	4 (33.3%)
G/G+G/T	43 (53.8%)	8 (66.7%)
	$\chi^2=0.7, d=1, p=0.4$ 1.3 (0.6–2.4, p=0.4)	
Genotypes	AMVC patients Aorta or mitral valves calcified	AMVC patients Aorta and mitral valves calcified
VDR rs1544410 BSM1		
G/G	27 (38%)	5 (50%)
A/A+A/G	44 (62%)	5 (50%)
	$\chi^2=0.52, d=1, p=0.4$ 0.7 (0.4–1.5, p=0.4)	

role of genetic in CVD susceptibility is confirmed, there is no approved evidence correlated with vitamin D deficiency, VDR and VDBP genetic variations with increased the risk of CVD. Association of vitamin D deficiency with autoimmune diseases, certain cancers, osteoporosis, hypertension, preeclampsia, diabetes, and hyperlipidemia has already been reported [25, 26].

Recently, evidence has demonstrated that the deficiency of vitamin D is correlated with the prevalence of CVD [25]. The genetic variation of VDBP, a major transporter of vitamin D metabolites, has been demonstrated to alter serum 25(OH) vitamin D levels [9]. According to our

knowledge, there are only a few reports regarding the association of VDR rs1544410G>A and VDBP rs7041T>G genes polymorphisms with susceptibility to CAD and AMVC. In the present study, for the first time, we have focused on the role of SNPs of VDR rs1544410G>A and VDBP rs7041T>G genes in susceptibility to CAD, AMVC and their effects on systolic and diastolic pressures, vitamin D, Ca, phosphate and lipid profile in a population from west of Iran. We detected that distribution of genotypes and alleles of VDR rs1544410G>A polymorphism was strongly higher in CAD patients and they enhanced the risk of CAD. The present study also suggests that the

Table 6 Carrier odds ratios interaction between VDBP rs7141T>G G allele and VDR rs1544410G>A, A allele in CAD patients and patients with mitral and aorta valve calcified compared with control group

VDBP T7041G	VDR G1544410A	CAD patients	Control group	OR(95%CI)	
G	A				
–	–	n=12 (7.6%)	n=17 (9.5%)	References	
+	–	n=28 (17.8%)	n=52 (26.8%)	0.78 (0.3–1.9, p=0.5)	($\chi^2=0.3$, df=1, p=0.578)
–	+	n=30 (19.1%)	n=29 (16.1%)	1.22 (0.8–1.9, p=0.39)	($\chi^2=0.72$, df=1, p=0.4)
+	+	n=87 (55.4%)	n=84 (45.8%)	1.15 (0.9–1.5, p=0.32)	($\chi^2=1$, df=1, p=0.3)
VDBP 70410G	VDR G15444100A	AVC and MAC	Control group	OR(95% CI)	
G	A				
–	–	n=13 (16%)	n=17 (9.5%)	References	
+	–	n=19 (23.5%)	n=52 (28.8%)	0.49(0.2–1.2, p=0.11)	($\chi^2=2.5$, df=1, p=0.11)
–	+	n=23 (28.4%)	n=29 (16.1%)	1.02(0.6–1.9, p=0.92)	($\chi^2=0.1$, df=1, p=0.92)
+	+	n=26 (32.14%)	n=84 (45.8%)	0.74 (0.58–1, p=0.044)	($\chi^2=4.2$, df=1, p=0.041)

VDBP rs7041T>G G allele and VDR rs1544410G>A A allele in AVC and MVC patients was significantly differences ($\chi^2 = 9.2$, df = 3, p = 0.027) but in CAD patients was not significantly differences ($\chi^2 = 6.3$, df = 3, p = 0.1)

Table 7 The distribution of Vitamin D deficiency between CAD, AMVC and control group

Vitamin D modified	AMVC patients	Control	CAD patients	Control	CAD patients	AMVC patients
Sever deficient < 10 ng/mL	51 (55.4)	70 (38.5)	55 (35)	70 (38.5)	55 (35)	51 (55.4)
Deficient 10 < ng/mL > 20 ng/mL	24 (26.1)	39 (21.4)	57 (36.3)	39 (21.4)	57 (36.3)	24 (26.1)
Insufficient 20 < ng/mL > 30	8 (8.7)	44 (24.2)	24 (15.3)	44 (24.2)	24 (15.3)	8 (8.7)
> 30 ng/mL	9 (9.8)	29 (15.9)	21 (13.4)	29 (15.9)	21 (13.4)	9 (9.8)
	$(\chi^2 = 13.9$, df = 3, p = 0.003)		$(\chi^2 = 10.5$, df = 3, p = 0.01)		$(\chi^2 = 10.1$, df = 3, p = 0.01)	

A allele of VDR gene at position rs1544410 could be a suitable marker for prediction of CAD development.

Consistent with our results, VDR polymorphism has been shown to strongly increase the risk of calcific aortic valve stenosis in German [27]. Elevated risk of CAD in Caucasian population associated with VDR Bsm1 allele and genotype has also been reported by Shuai et al. [12]. However, in contrast to our results, Alizadeh et al. failed to indicate such an association in East-Asians population [28]. In addition, no strong association has been found between VDR SNP/haplotypes with either Vit D or CAD in Indian population [20].

In addition, higher systolic and diastolic blood pressure and FBS, urea and creatinine levels in CAD patients was strongly correlated with wild and heterozygote genotypes of VDR rs1544410G>A gene. Our results indicated that GG and GA+AA genotypes of VDR at position rs1544410 were considerably associated with higher levels of phosphate, FBS, urea and also higher systolic and diastolic blood pressures in patients with AMVC compared to control group.

We also found that the VDBP rs7041T>G gene polymorphism had strongly protective role against the incidence of AMVC in Iranian population. The dominant genotype T/T+G+G/G genotype and G allele of VDBP at position rs7041 had protective role against the incidence of AMVC. Changes in VDBP protein due to rs7041T>G mutation might be responsible for its protective role in AMVC. Decreased risk for AMVC susceptibility was observed in presence of both G allele or VDBP and the A allele of VDR rs1544410. There is no study demonstrating the influence of VDBP rs7041T>G gene polymorphism in CAD or in AMVC susceptibility. In the report of Chan et al. the effect of 4 SNPs, rs4588, rs7041, rs2282679, rs1155563 of VDBP gene were investigated and their findings indicated that these SNPs were correlated with serum concentration of 25(OH)D and genetically deprived vitamin D predisposes the individuals with CAD to increased atrial fibrillation (AF) [29].

The high serum levels of FBS, urea and creatinine serum level and systolic and diastolic blood pressures in CAD patients compared to control were also associated

with the VDBP rs7041 TT genotype in dominant genetic model. Further, the increased BMI and LDL-C concentration in CAD and in AMVC patients were associated with T/G+G/G genotype of VDBP 7rs7041T>G.

Our results also indicated that serum concentration of vitamin D in CAD and in AMVC patients was lower than in control subjects. The presence of TT and T/G+G/G genotypes of VDBP rs7041T>G strongly affected the vitamin D concentration in CAD and AMVC patients compared to their corresponding control groups. AMVC patients with VDR rs1544410 GG and G/A+A/A genotypes had also lower level of vitamin D concentration than their corresponding control subjects. Our findings suggest that correlation of deficiency of vitamin D with VDR rs1544410>A and VDBP gene rs7041T>G polymorphisms may be one of the important factors that increase the CAD and AMVC incidence in population from west of Iran.

Daffara et al. reported the impact of VDBP polymorphisms rs7041 and rs4588 on the coronary artery disease extent in Italian population and they found that the status of 25(OH) D but no genetic variants of VDBP were correlated with CAD [30]. Mostafavi et al. indicated that although the deficiency of vitamin D was detected in 60.2% of the 224 Iranian patients with coronary artery stenosis, low level of vitamin D did not correlate with persistence, extent, and severity of the disease [31]. According to the report of Akin, Shanker, Young and Sun et al. Vitamin D deficiency was strongly increased the risk of coronary artery stenosis and CAD among populations from Turkey, Colorado (United States), India and china [20, 32–34], respectively. These inconsistent findings may be due to factors associated with the study designs, ethnicity, sample size, and other CAD and AMVC risk factors. Further study is needed to confirm this correlation.

Conclusion

This study showed that SNPs at position rs1544410 of VDR and at position rs7041 of VDBP genes may be risk factors for CAD development and SNP at position 7904 of VDBP is protective for susceptibility to AMVC, respectively. In addition, these SNPs were associated with vitamin D deficiency in CAD and AMVC patients. Both VDR rs1544410G>A and VDBP 7041T>G SNPs had strong effect on FBS, urea and creatinine concentrations in CAD and AMVC patients.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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