Clinical and Experimental Health Sciences

VDBP and VDR Mutations May Cause In-Stent Restenosis

Deniz Kirac[1], Aysun Erdem Yaman[2], Hazal Gezmis[1], Kemal Yesilcimen[2], Tuba Avcilar[3], Ahmet Ilter Guney[3], Elif Cigdem Keles[4], Gulsah Koc[5], Rabican Akkanat[3], Turgay Isbir[1]

[1] Yeditepe University, Faculty of Medicine, Department of Medical Biology, Istanbul, Türkiye.
[2] Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology, Istanbul, Türkiye.
[3] Marmara University, Faculty of Medicine, Department of Medical Genetics, Istanbul, Türkiye.
[4] Yeditepe University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Istanbul, Türkiye.
[5] Istanbul Aydin University, Faculty of Medicine, Department of Medical Biology, Istanbul, Türkiye.

Correspondence Author: Deniz Kirac
E-mail: denizyat@hotmail.com
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ABSTRACT

Objective: In-stent restenosis (ISR) is the narrowing of a stented coronary artery lesion. A considerable number of patients undergoing percutaneous coronary intervention (PCI) are affected by ISR. The predominant mechanism in the development of ISR is an inflammatory response to vessel wall injury during PCI. Vitamin D is reported to have anti-inflammatory properties, so it may also be related with ISR. Therefore, in this study the relationship between vitamin D receptor *(VDR)*, vitamin D binding protein *(VDBP)* gene variations and ISR were investigated.

Methods: Fifty-eight ISR patients who have chest pain, underwent angiography and were found to have restenosis in the previously inserted stent were included in the patient group and thirty-five patients who have chest pain and were not found to have restenosis in their previous stent in coronary angiography were included in the control group. rs7041 and rs4588 variations in *VDBP*; rs1544410 and rs2228570 variations in *VDR* were investigated by real-time polymerase chain reaction (RT-PCR). Results were evaluated statistically.

Results: The CC genotype of rs2228570 variation of *VDR* and the CA genotype of rs4588 variation of *VDBP* were found statistically high in patient group. rs7041 variation was found statistically high in patients who had myocardial infarction history before stent implantation. Additionally, it was demonstrated that vitamin D deficiency (vitamin D level<20 ng/ml) was found statistically high in patient group.

Conclusion: It was considered that rs2228570, rs4588 variations and the presence of vitamin D deficiency may play role in the formation of ISR.

Keywords: ISR, *VDR, VDBP*, RT-PCR

1. INTRODUCTION

Coronary artery disease (CAD) is a complex cardiovascular disorder which is related to pathophysiologic conditions, some environmental and genetic factors (1). Percutaneous coronary intervention (PCI) by balloon angioplasty and stenting have participated in the treatment of CAD, and have provided improvement in acute myocardial infarction (MI) (2). Unfortunately, a considerable number of patients undergoing PCI are affected by ISR (3-5). In-stent restenosis (ISR) was defined angiographically as the presence of >50% diameter stenosis at the stent site or within 10 mm proximal or distal to the stent. It is a complex disease considered to derive from several causative mechanisms, which have yet to be fully defined. The predominant mechanism in the development of ISR is an inflammatory response to vessel wall injury during PCI (6). Vitamin D is also reported to have anti-inflammatory properties, so it may also be related with ISR. Until now, vitamin D deficiency has been shown as a common risk factor for cardiovascular disease in several studies (7-9). 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), the active form of vitamin D, binds to vitamin D binding protein (VDBP) in order to transport vitamin D metabolites to target tissues. VDBP binds to vitamin D receptor (VDR) to produce a biological effect (10). 1,25$[OH]_2$D acts through a specific VDR, which is a hormone structure that communicates with the vitamin D responsive element of several target genes and regulates the transcription of more than 200 heterogeneous genes. Therefore, vitamin D have crucial roles in the regulation of vascular smooth muscle cell proliferation, cell differentiation, vascular calcification, and angiogenesis (4, 7, 8, 11). It has been suggested that some candidate gene polymorphisms involved in the process of ISR are also associated with vitamin D metabolism (12).

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The gene encoding human *VDR* is located on chromosome 12q12-q14, and has many common allelic variants (13). Two of the most common polymorphisms are named as *VDR FokI* (rs2228570) and *BsmI* (rs1544410) (14). Until now, only some studies have investigated the relationship between rs2228570, rs1544410 SNPs, vitamin D levels and the risk of CAD (15). To our knowledge these mutations were not investigated before for ISR. *FokI* polymorphism, which is located in exon 2 of a gene, identifies 2 translation initiation start sites (ATG) in the *VDR*. T>C polymorphism leads to shortening of the protein by three amino acids (16). Studies also show that *FokI* is a potential genetic marker for CAD. *Bsm*I (A>G) is located in intron 8 of *VDR*. It affects the mRNA stability and causes a reduction in VDR levels (17).

VDBP, also known as a human group specific component (GC globulin), has three common phenotypic alleles in chromosome 4. These alleles differ from one another by integrating two variants of *VDBP*: rs4588 and rs7041, which are both located in exon 11. rs7041 (G>T) encodes Asp432Glu and rs4588 (C>A) encodes Thr436Lys (18). It has been found that lower 1,25[OH]2D levels are associated with rs7041 and rs4588 (AA, AC) mutations (19).

In vivo vitamin D level is evaluated as normal (>30 ng/mL), insufficient (20–30 ng/mL) and deficient (<20 ng/mL) (10, 20). In this study vitamin D leves were also measured to investigate the relationship between vitamin D levels and ISR.

Until today, genetic factors that may be related with ISR could not be completely defined. Thus, in this study the effects of *VDR* and *VDBP* variations to ISR were investigated.

2. METHODS

2.1. Study Population

In this prospective study, 58 consecutive patients who applied to the cardiology outpatient clinic of Dr. Siyami Ersek Training and Research Hospital with chest pain, underwent angiography and were found to have restenosis in the previously inserted stent were included in the patient group. All coronary angiography procedures were performed via the femoral route of patients (Siemens Axiom Artis Zee, Germany). The diagnosis of ISR was performed by expert invasive cardiologists. Thirty-five consecutive patients who applied to the cardiology outpatient clinic with chest pain and were not found to have restenosis in their previous stent in coronary angiography were included in the control group. Patients who have kidney or liver disease, acute coronary syndrome, hyperparathyroidism, history of malignancy of use of drugs including calcium (Ca) and vitamin D were excluded from the study.

The present study protocol was approved by the Institutional Ethics Committee of Yeditepe University (Approval Date:22.06.2015, Approval Number:495). Written informed consent from participants was obtained following a detailed explanation of the experimental procedures.

2.2. Biochemical Analysis:

The blood samples were obtained at the time of angiographic procedures and biochemical parameters such as vitamin D, lipid and hemoglobin levels were measured (Coulter LH780, Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Vitamin D deficiency is defined as Vitamin D levels smaller than 20 ng/mL (10,20). All patients were prescribed statins, beta-blockers and acetylsalicylic acid, according to their electronic prescriptions.

2.3. Molecular Analysis

After blood samples were obtained from all patients, genomic DNA was isolated from 200 µl blood by using commercially available kits according to manufacturers' instructions (Roche, Basel, Switzerland). DNA concentrations were determined with a NanoDrop spectrophotometer (Thermo Scientific, Foster City, CA, USA). DNA samples with a DNA concentration greater than 30 ng/µL and OD260/280 ratio near to 1.8 were used for molecular analysis. rs7041 and rs4588 variations in *VDBP;* rs1544410 and rs2228570 variations in *VDR*; were analyzed by using Real-time PCR (RT-PCR) (Applied Biosystems, Foster City, CA, USA). RT-PCR Assay ID's and primer sequnces of variants which were attached with VIC and FAM fluorescent material are shown in Table 1. The RT-PCR cycle parameters for all variants were 60^{0}C for 1 min., 95^{0}C for 10 min. followed by forty cycles of 95^{0}C for 15 sec. and 60^{0}C for 1 min., then 60^{0}C for 1 min.

Table 1. *Primer sequnces of variants which are attached with VIC and FAM fluorescent material*

SNP ID (Assay ID)	Gene	Primer sequences of variants which are attached with VIC and FAM fluorescent material
rs7041 (C___3133594_30)	VDBP	GCTTTGCCAGTTCCGTGGGTGTGGC**[A/C]** TCAGGCAATTTTGCTTTTAGTCGCT
r4588 (C___8278879_10)	VDBP	CTTGTTAACCAGCTTTGCCAGTTCC**[G/T]** TGGGTGTGGCATCAGGCAATTTTGC
rs1544410 (C___8716062_10)	VDR	GAGCAGAGCCTGAGTATTGGGAATG**[C/T]** GCAGGCCTGTCTGTGGCCCCAGGAA
rs2228570 (C__12060045_20)	VDR	GGAAGTGCTGGCCGCCATTGCCTCC**[A/G]** TCCCTGTAAGAACAGCAAGCAGGCC

2.4. Statistical Analysis

Statistical Package for the Social Science (SPSS) 23.0 was used to analyze the results. Assumption of normal distribution was checked with the Kolmogorov-Smirnov test. Two independent samples t test was used to compare continuous variables' means between two groups which were normally distributed. Kruskal Wallis tests were performed to investigate the difference between genotypes and risk factors (which are not normally distributed) of ISR. If there were statistically significant differences for pairwise comparison, Mann-Whitney U test was performed and Bonferroni correction

was applied to p values. p values smaller than 0.05 (p<0.05) were considered as statistically significant.

3. RESULTS

3.1. Study Population

The baseline characteristics of the study population are shown in Table 2. When groups were compared according to the baseline characteristics; vitamin D, white blood cell (WBC) and hemoglobin levels were found statistically low whereas the presence of vitamin D deficiency (vitamin D level<20 ng/mL), family history of CAD, hypertension and C reactive protein (CRP) levels were found statistically high in patient group (p<0.05). Other parameters, which are shown in table 2 were not found statistically significant (p>0.05).

Table 2. *Baseline characteristics of the study population.*

Baseline Characteristics	Groups (number of participants)		p values
	Control group (n=35)	Patient group (n=58)	
Vitamin D level (ng/mL)	18.07 ± 4.97	12.10 ± 4.44	**<0.001****
Age (years)	59.17 ± 10.36	59.52 ± 8.80	0.86
Hyperlipidemia (%)	12 (34.3%)	29 (50%)	0.14
Total cholesterol (mg/dl)	180.63 ± 47.10	184.90 ± 42.54	0.65
Triglyceride (mg/dl)	166.17 ± 101.86	179.64 ± 123.20	0.59
WBC (x1000/ml)	9.12 ± 2.77	7.84 ± 2.59	**0.027***
HbA1c (%)	6.13 ± 1.22	6.65 ± 1.79	0.13
Hypertension (%)	14 (40%)	38 (65.6%)	**0.016***
Current smoking (%)	11 (31.4%)	20 (34.5%)	0.76
Diabetes mellitus (%)	11 (46.6%)	27 (31.4%)	0.15
Familial history of CAD (%)	19 (54.3%)	55 (94.8%)	**<0.001****
CRP (mg/ml)	0.92 ± 0.53	1.40 ± 0.9	**0.005***
Hemoglobin	14.02 ± 1.27	13.04 ± 2.46	**0.013***
Serum creatinine (mg/dl)	0.95 ± 0.21	1.02 ± 0.65	0.54
Total thrombocytes (ml)	239.80 ± 78.85	231.81 ± 58.04	0.58
Vitamin D deficiency	18 (51.4%)	54 (93.1%)	**<0.001****
COPD	7 (20%)	7 (12.1%)	0.30

**p<0.05, **p<0.001, HbA1c: Hemoglobin A1c, WBC: White blood cell, CAD: Coronary artery disease,*
CRP: Creactive protein, COPD: Chronic obstructive pulmonary disease

3.2. VDBP and VDR genotyping

The genotype distributions of study groups are shown in table 3. The CC genotype of variation of *VDR* and the CA genotype of rs4588 variation of *VDBP* were found statistically high in patient group (p<0.05). However rs7041 of *VDBP* and rs1544410 of *VDR* were mostly detected in patient group, they were not found statistically significant (p>0.05).

Table 3. *Genotype distributions of study groups*

Gene names and genotype distributions	Groups		p values
	Control group (n=35)	Patient group (n=58)	
VDBP			
rs4588			
CC	29 (82.9%)	34 (58.6%)	
CA	6 (17.1%)	20*(34.5%)	**0.036***
AA	0 (0%)	4 (6.9%)	
rs7041			
GG	10 (28.6%)	9 (15.5%)	
GT	10 (28.6%)	30 (51.7%)	0.076
TT	15 (42.9%)	19 (32.8%)	
VDR			
rs2228570			
TT	7 (20%)	1 (1.7%)	
TC	10 (28.6%)	22 (37.9%)	**0.009***
CC	18 (51.4%)	35* (60.3%)	
rs1544410			
GG	8 (22.9%)	26 (44.8%)	
GA	21 (60%)	25 (43.1%)	0.103
AA	6 (17.1%)	7 (12.1%)	

**p<0.05*

3.3. Statistically Significant Assocations Between Risk Factors and Variations

All of the risk factors which are shown in table 2, were also analyzed for investigating the association between these factors with variations. Of these, rs7041 variation was found statistically high in patients who had myocardial infarction history before stent implantation (p=0.048). (Figure 1). The other factors were not found statistically significant (p<0.05).

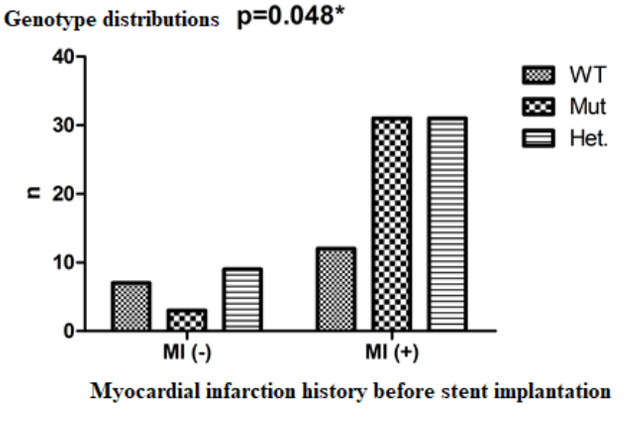

Figure 1. *Association between myocardial infaction (MI) history before stent implantation with rs7041 variation*

4. DISCUSSION

Mortality due to cardiovascular disease has risen day by day, and it is estimated that it may increase to 23.4 million deaths by the year 2030 (21). Although PCI is a reliable application to treat CAD, development of restenosis is a major problem after angioplasty (22). CAD can occur due to platelet activation, thrombus formation, endothelial dysfunction, activation in vascular smooth cell presentation or inflammation. It is demonstrated that vitamin D affects the renin-angiotensin system (RAS), and that vitamin D deficiency causes inflammation (23). Functional abnormality in endothelial cells takes place before and throughout the development of atherosclerosis, and especially during plaque fracture. Oxidized LDL appears to induce this cellular dysfunction. High levels of angiotensin II facilitates oxidation of LDL and its uptake by receptors on monocytes, macrophages and endothelial cells (24). Also RAS contributes to the development of arterial hypertension. In a brief study, it was shown that vitamin D could reduce high blood pressure in hypertension patients (25). This might be explained by the observation of endothelial dysfunction involved in both hypertension and restenosis. A recent study also showed that lower vitamin D level (<30 ng/ml) is related with CAD (21). It is suggested that vitamin D intake limits neointimal formation following coronary intervention, and provides protection against the development of coronary restenosis (8, 22). Vitamin D deficiency may also induce the production of C reactive protein (CRP), which is known to be directly related with the inflammation process (23, 24). According to these findings, it was considered that there might be an association between vitamin D deficiency and restenosis progression related with inflammation. At the end of the study, vitamin D deficiency (vitamin D level<20 ng/mL) was found statistically high in in ISR patients ($p<0.001$). Additionally hypertension and CRP level were also found statistically high in patient group ($p<0.05$).

ISR is the main obstacle of percutaneous coronary intervention. Heritable factors also may have a role in ISR. Many studies showed that investigating the effect of related genes and other risk factors on the development of restenosis has critical importance for new therapeutic approaches. *VDR* and *VDBP* polymorphisms have important impact on the regulation of vitamin D metabolism (19). Excluding vitamin D deficiency, *VDR* and *VDBP* genes are also the main regulators in vitamin D metabolism (10). Therefore, these main factors should be investigated together in order to evaluate the relationship between ISR and genes related with vitamin D metabolism. In our study, the CC genotype of rs2228570 variation of *VDR* and the CA genotype of rs4588 variation of *VDBP* were found statistically high in patient group ($p<0.05$). Contrary to these findings, in a separate study no significant association was found between these polymorphisms with ISR (25,26).

In the present study, the relationship between ISR and other risk factors were also investigated. Recent studies have shown that there is a relationship between vitamin D level and MI (27). Similarly, according to our results rs7041 variation was found statistically high in patients who had myocardial infarction history before stent implantation ($p=0.048$). Contrary to this finding, in another study no significant associations were found between MI, type 2 diabetes mellitus, death, BMI, lipid levels, blood pressure and HbA1c (28).

Multiple studies have shown that vitamin D deficiency is a risk factor for cardiovascular diseases (7, 9). Growing evidence has supported that vitamin D plays a critical role in modulating the anti-inflammation in other inflammatory diseases such as ulcerative colitis (UC). Recent studies suggest that UC is characterized by relapsing inflammatory process in the gastrointestinal tract; it is highly related with vitamin D metabolism and its regulator protein VDR due to its anti-inflammation effect (29, 30). Similarly, in the present study it was found that ISR, which is related with inflammation, has an association with vitamin D deficiency

5. CONCLUSION

According to these findings, it was considered that gene variations which are related with vitamin D metabolism and vitamin D deficiency may increase the risk of ISR. In conclusion, genetic screening of patients for VDR and VDBP variations before stent implantation may provide information about the possibility of ISR. Possible tracking of gene variations and risk factors with some other studies with high number of patients may help to clarify the mechanism of ISR.

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