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Full Length Research Paper

Association between Vitamin D Receptor BsmI (rs1544410) gene Polymorphism and Parathormone Level in Patients on Haemodialysis

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Abstract

Background: *Low active vitamin D is fully known to play a significant role in the pathogenesis of hyperparathyroidism. Studies suggested possible effect of vitamin D receptor (VDR) gene polymorphisms on the control of the calcium-PTH-vitamin D axis which proved relevant in hemodialysis patients.* ***The aim of the study:*** *was to detect the frequency of VDR Bsm 1 (rs1544410) gene polymorphism in an attempt to reveal possible relation between the presence of the polymorphism and Parathormone (PTH), calcium, and phosphate serum levels in patients on dialysis.* ***Subjects and Methods:*** *Forty patients with chronic kidney disease (CKD) on hemodialysis and 50 controls were included. Serum levels of calcium, phosphorus, and PTH were detected. Detection of VDR Bsm1 (rs1544410) gene polymorphism was analyzed using Polymerase Chain Reaction using specific restriction enzymes and Restriction Fragment Length Polymorphism (PCR-RFLP).* ***Results:*** *Phosphorus and PTH levels were significantly higher in cases than controls ($p < 0.001$). The Bsm1 genotype distribution among cases was; 22.5% bb, 50.0% Bb and 27.5% BB. Patients had significantly higher presentation of the bb genotype than control group ($p=0.01$). Moreover, more carriers of the bb genotype were detected among patients with high PTH level but this difference didn't reach significance ($p=0.272$). There was no association found between PTH level and different genotypes.* ***Conclusion:*** *VDR VDRBsm 1 (rs1544410) gene polymorphism was significantly higher in patients. Moreover, none of the detected genotypes showed increased risk of high PTH level.*

Key words: *CKD, PTH, gene polymorphism, VDR, Bsm1*

Introduction

Chronic kidney disease (CKD) has several effects on bone mineral metabolism from the early stages of the disease. This entity is known as mineral and bone disorders, chronic kidney disease (CKD-MBD). It usually manifests as metabolic changes in calcium, phosphorus, vitamin D and parathyroid hormone (PTH), with or without alterations in histology, linear growth or bone strength. Vascular or soft tissue calcifications might be one of the manifestations *(1).*

Homeostasis of calcium and phosphorus involve the parathyroid gland, intestine, kidney and bone, which are the major bodily reservoirs of calcium and phosphorus *(2).* It is known that vitamin D exists as an ergocalciferol (vitamin D2) in plants or as cholecalciferol (vitamin D3) in animal tissues *(3).*Both these forms are biologically inactive (pro-hormones) and must be hydrolyzed in the liver as carbon 25. Once hydrolyzed, they give rise to 25-hydroxyvitamin [25(OH) D3], which is the most abundant metabolite of vitamin D,25(OH)D3 when transformed into 1,25 dihydroxycholecalciferol or calcitriol (active vitamin D) then acts in its physiological role as a hormone*(4&5).*

This process occurs mainly in the proximal renal tubules by the action of the enzyme 1α-hydroxylase (CYP27B1), the effects of calcitriol are regulated by binding to its specific nuclear steroid receptor known as vitamin D receptor (VDR). VDR is located in many cells in the kidneys as well as in other target tissues as the parathyroid gland, bone, heart, intestine, endothelial cells, lymphocytes, megakaryocytes and pneumocytes. *(6,7&8).* In bone tissues, VDR activation increases the expression of fibroblast growth factor (FGF23) and stimulates resorption of bone calcium deposits. In the parathyroid gland VDR blocks the transcription of the PTH gene and in turn increases calcium absorption in the intestine *(2).*

It has also been reported that VDR modulates the transcription of genes that alter histones.VDR gene is located on chromosome 12 (12q13.11) with 11 exons and four polymorphic regions. The deleterious mutations in the VDR gene cause calcitriolresistant rickets, a rare monogenic disease*(9,10).* The regulation of the calcium-PTH-vitamin D axis for the potential effect of VDR gene polymorphisms is highly relevant in chronic kidney disease*(11).*We also know that there are several polymorphisms detected by restriction enzymes: *BsmI*(for rs1544410), *ApaI*(for rs7975232)and *TaqI*(for rs731236) .These polymorphisms are located in the

3' region of intron 9 and exon 10 of the VDR gene (*Ensembl*: ENSG00000111424). The possible influence of polymorphisms of the gene that encode the VDR for the regulation of the biological processes is particularly important in patients with CKD in which alterations have been described, in both parathyroid VDR content as well as in its functionality, which modify the transcriptional activity of this gene *(10).*

Available information on the influence of these polymorphisms and bone density varies depending on the series consulted. In the case of *BsmI*, the wild-type allele is associated with higher values of bone mass. It has been reported that, in patients on hemodialysis who are homo- and heterozygous for the b allele have higher levels of PTH than homozygous BB patients and BB carriers require less parathyroidectomies*(12).*

VDR polymorphisms have also been associated with autoimmune diseases such as multiple sclerosis and type 1 diabetes mellitus, as well as other acquired diseases such as hypertension cancer, remineralization and bone density (*13&14).*
The aim of this study was to describe the frequency of polymorphism rs1544410 (*BsmI*) in the VDR and its relation to some biochemical markers (PTH, phosphorus, serum calcium) in patients with CKD.

Patients and Methods
This study included forty patients with end stage renal disease on maintenance haemodialysis for more than six months. They were selected from the Nephrology and Haemodialysis unit ofBeni-Suef University. The dialysis sessions for these patients were three times weekly and the duration of each session was four hours. Fifty apparently healthy subjects of comparable age and socioeconomic status were included as control group. Exclusion of patients with any clinical state that might affect intact parathyroid hormone (iPTH) values (e.g., granulomatous disease or neoplasms) or with history of surgical or chemical parathyroidectomy. All patients were subjected to detailed history taking and complete physical examination.

Laboratory investigations:serum levels of glucose, urea, creatinine, uric acid, albumin, total cholesterol, low and high density lipoprotein cholesterol, calcium, phosphorus, C- reactive protein.2 ml of venous blood were put in Ethylene Diamine Tetraacetic Acid (K_3 EDTA) vacutainer tube and the plasma was separated immediately and used for the determination of parathyroid hormone level.

The levels and activities of the clinical chemistry analytes were conducted on the Olympus AU400 clinical chemistry Autoanalyzer (Beckman Coulter Inc.) and was calibrated using Olympus multicalibrator. While serum intact PTH analysis was performed on the Cobas e411 immunoassay analyzer (Roche Healthcare and Diagnostics). DNA extraction: EDTA- whole blood was used. Samples were frozen at –20°C till used for DNA extraction. DNA was purified using Gene JET™ Genomic DNA purification Kit **Cat. N^{O}K0721**(Fermentas – Thermo, USA). The extract was kept frozen at –20°C till time of polymerase chain reaction (PCR).The concentration and purity of the genomic DNA was measured on a nanodrop 1000 spectrophotometer (Thermo scientific, USA) at 260 and 280 nm.

PCR amplification:A pair of specific primers flanking the SNP region in intron 8 were used. The lyophilized primers were reconstituted by addition of sterile water to give a final concentration of 100 pmoles/ µL for each and stored at –20°C. **Primers for BsmI:** Forward primer: 5'-CAACCAAGACTACAAGTACCGCGTCAGTGA-3', Reverse primer: 5'-AAC CAG CGG GAA GAG GTC AAG GG-3', (Fermentas – Thermo, USA). Total reaction volume of 25ul as follows: 12.5ul DreamTaq™ Green PCR Master Mix **#K1081 (Fermentas – Thermo, USA)**, 10 ul extracted DNA, Forward and reverse primer 0.5ul each and 1.5 ul nuclease free water. Tubes were transferred to the thermal cycler (Quanta Biotech, UK) where the PCR conditions were adjusted as follows: initial denaturation for 3 min at 95 ^{0}C, 30 cycles of amplification, annealing was at 61.5 ^{0}C and final extension10 min at 72 ^{0}C. PCR products were applied on a 2% agarose gel containing 10 µL ethidium bromide along with a 1000-50 Gene Ruler 50 bp DNA ladder.

Genotyping: Restriction digestion of PCR products using Fast Digest Mva 1269I (BsmI) #FD0964. Genotypes were detected as homozygous BB, heterozygous Bb, and homo mutant bb with PCR products were detected at 825 bp

Statistical analysis:
Data were analyzed using the software, Statistical Package for Social Science, (SPSS) version 19. Frequency distribution with its percentage and descriptive statistics with mean and standard deviation were calculated. Chi-square, t-test, correlations were done whenever needed. P values of less than 0.05 were considered significant.

Results
This study included forty patients with end stage renal disease on maintenance haemodialysis for more than six months, their mean age was 51.00±6.48 years. The Control groupconsisted of 50 apparently healthy volunteers of comparable age and socioeconomic status of the patients group, their mean age was 50.60±5.93 years. There was no statistically significant difference found, between patients group and the control group regarding age and sex distribution. The Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Mean blood pressure (MBP) were significantly higher in patients group than in control group (p=0.006, 0.003 and 0.003) respectively, Table (1).

Moreover Results demonstrated that urea and creatinine serum levels were statistically higher in cases than in control group (p<0.001). phosphorus levels were significantly higher in cases 6.03 ± 1.38 mg / dl than controls 3.64 ± 0.31 mg / dl (p<0.001). On the other hand, albumin, calcium and corrected calcium levels were significantly lower among cases (p < 0.05).While calcium-

phosphorus product (Ca-P product) was much higher in cases than controls ($p < 0.001$). Besides, PTH levels recorded very high figures in cases than controls; 407.42 ± 306.60pg / dl in cases and 22.28± 3.10 pg / dl in controls ($p < 0.001$) Table (2).

The compared to 4.0% for bb, 58.0% for Bb and 38.0% for BB in controls. Comparing the genotype frequency in the two groups revealed that patients had significantly higher presentation of the bb genotype (p=0.01) the Bb and BB genotypes didn't show significant difference genotypes distribution among cases was; 22.5% bb, 50.0% Bb and 27.5% BB between both groups (p=0.449&0.294 respectively) Table(3).

There was no statistically significant difference between patients carrying different genotype and their mean serum levels of any of calcium (p=0.312) corrected calcium (p=0.326), phosphorus (p=0.923), calcium phosphorus (Ca-P) product (p=0.793) or PTH level (p=0.997) Table (4). There were no statistically significant correlations between the genotype of cases and any of calcium, corrected calcium, phosphorus, calcium phosphorus (Ca-P) product or PTH levels in serum Table (5).

Our results showed that although that patients having a PTH level > 300 pg/ml had a higher frequency of both *bb* and *BB* genotypes (77% and 63.4%, respectively), yet this didn't show a statistical difference when compared to genotype distribution among patients with PTH level < 300 pg/ml Table (6). Moreover, the frequency of bb genotype among patients with PTH>300pg/ml (29.2%) was higher than the other group (12.5), yet no association was found between the PTH level and the presence of the bb genotype (p=0.272, OR 2.882 CI 95% 0.514-16.150) Table (7).

Table 1: Demographic data of study groups

	Cases (n=40)	Control (n=50)	p value
Age (year) Mean ± SD	51.00±6.48	50.60±5.93	0.860
Sex Male/Female (%)	55/45%	70/30%	0.312
SBP (mmHg) Mean ± SD	127.00±14.88	113.00±6.75	**0.006***
DBP (mmHg) Mean ± SD	83.00±8.83	74.00±5.16	**0.003***
MBP(mmHg) Mean ± SD	97.66±10.45	86.98±5.08	**0.003***

*SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, SD: standard deviation, *p value: significant if <0.05.*

Table 2: Laboratory parameters of study groups

Parameters	Cases (n=40) mean±SD	Control (n=50) mean±SD	p value
Urea(mg/dl)	165.60±34.23	36.10±5.72	<0.001*
Creatinine (mg/dl)	10.90±2.93	0.96±0.16	<0.001*
Albumin (g/dl)	3.85±0.29	4.32±0.25	<0.001*
Calcium(mg/dl)	8.79±0.91	9.46±0.36	0.029*
Corrected calcium (mg/dl)	8.91±0.92	9.20±0.25	0.034*
Phosphorus (mg/dl)	6.03±1.38	3.64±0.31	<0.001*
Ca-P product (mg^2/dl^2)	53.83±13.94	33.44±2.61	<0.001*
PTH (pg/ml)	407.42±306.98	22.28±3.10	<0.001*

**p value: significant if <0.005, Ca-P product: calcium phosphorus product, PTH: parathyroid hormone.*

Table 3: BsmI Genotype frequencies among the studied groups

Genotype	Cases (n=40) NO (%)	Control (n=50) NO (%)	P value
bb	9 (22.5%)	2 (4%)	0.01*
Bb	20 (50%)	29(58%)	0.449
BB	11 (27.5%)	19 (38%)	0.294

**p value: significant if <0.05*

Table 4: Laboratory findings in different Genotypes:

Parameters	Genotype Mean ± SD			p value
	bb (n.=9)	**Bb (n.=20)**	**BB (n.=11)**	
Calcium (mg/dl)	9.03±0.44	8.88±0.90	8.45 ±1.17	0.312
Corrected calcium (mg/dl)	9.07±0.42	9.04±0.92	8.55 ±1.16	0.326
Phosphorus (mg/dl)	5.87±1.69	6.09±1.19	6.07±1.54	0.923
Ca-P product (mg^2/dl^2)	53.19±15.67	55.28±13.45	51.73±14.46	0.793
PTH (pg/ml)	413.51±214.56	407.73±368.61	401.87±269.19	0.997

*Ca-P product: calcium phosphorus product, PTH: parathyroid hormone, *p value: significant if <0.05.*

Table 5: Comparing calcium parameters in different *Bsmi* Genotypes

Parameters	Genotype Mean ± SD			p value
	bb (n.=9)	Bb (n.=20)	BB (n.=11)	
Calcium (mg/dl)	9.03±0.44	8.88±0.90	8.45 ±1.17	0.312
Corrected calcium (mg/dl)	9.07±0.42	9.04±0.92	8.55 ±1.16	0.326
Phosphorus (mg/dl)	5.87±1.69	6.09±1.19	6.07±1.54	0.923
Ca-P product(mg^2/dl^2)	53.19±15.67	55.28±13.45	51.73±14.46	0.793
PTH (pg/ml)	413.51±214.56	407.73±368.61	401.87±269.19	0.997

*Ca-P product: calcium phosphorus product, PTH: parathyroid hormone, *p value: significant if <0.005.*

Table 6: Comparing BsmI Genotypes frequencies in patients with PTH level < 300 pg/mL > 300 pg/mL

	Genotype n (%)			p value
	bb (n=9)	Bb (n=20)	BB (n=11)	
PTH level < 300 pg/ml (n=16)	2 (22.2%)	10 (50%)	4 (36.4%)	0.354
PTH level > 300 pg/ml (n=24)	7 (77.8%)	10 (50%)	7 (63.6%)	

*PTH: parathyroid hormone, *p value: significant if <0.005*

Table 7: Association between BsmI Genotypes and PTH level

		PTH level > 300		PTH level < 300		P value	OR	95%CI	
		N=24	%	N=16	%			lower	upper
Genotype	**bb**	7	29.2%	2	12.5%	**0.272**	2.882	0.514	16.150
	Bb	10	41.7%	10	62.5%	**0.197**	0.429	0.117	1.568
	BB	7	29.2%	4	25.0%	**1**	1.235	0.295	5.181

Discussion

Chronic kidney disease affects almost every cell in the body through influencing bone and mineral metabolism. Calcium, phosphorus, PTH and vitamin D have been shown to be important determinants of survival associated with kidney disease *(15).*

The genetic influences determining the development and the severity of hyperparathyroidism secondary to renal failure are largely debated. In end-stage renal disease (ESRD) patients, the synthesis of vitamin D is defective and active vitamin D level is lowering as kidney function becomes progressively worse and begin to be very low *(16).* This lowering active vitamin D is well known to play a significant role in the pathogenesis of hyperparathyroidism *(17).*Interestingly; there are great differences in the degree of secondary hyperparathyroidism in ESRD patients. Whilst some patients improve severe and not controllable hyperparathyroidism, others improve only modestly increased levels that fail to elevate adequate bone turnover and outcome in bone disease. The reasons for this heterogeneous clinical behavior are not well defined *(18).*

On the other hand, VDR is a significant element for physiologic regulation of parathyroid role and is answerable for the inhibitory influence of vitamin D on parathyroid hormone secretion and parathyroid cell proliferation. In addition, reduced activation of VDR in the parathyroid glands drives to development release of PTH. This effect can be explained by the modifying role of VDR on calcium sensing receptors expressed in parathyroid glands. These calcium sensing receptors, which are known to react rapidly to extracellular calcium concentration and low calcium level, lead to further increase in the release of PTH and consequently hyperparathyroidism *(19).*

Meanwhile, it was suggested that VDR gene polymorphism seems to play a role in the response of parathyroid function among patients with ESRD and might introduce an explanation to this wide clinical variation *(16).* Inadequate vitamin D is an important factor in many of the complications in hemodialysis patients. However, although most of these patients receive vitamin D supplement, yet they may not show satisfactory clinical improvement. Many research has been carried out in chronic kidney failure and hemodialysis patients, therefore, study any connection among PTH levels and VDR polymorphisms*(20,21).*

Our study included 40 cases and 50 controls. The age of cases ranged between 41 and 61 years with a mean age of 51± 6.48 years while the age of controls ranged between 42 and 59 years with a mean age of 50± 5.93 years and there was no statistically significant difference between both groups regarding age (p>0.05). For the cases, the duration of dialysis ranged between one year and 19 years with a mean of 5.78 ± 4.48 years and their Hb levels ranged between 7.70 and 14.0 gm/dl with a mean of 10.52 ± 1.27 gm/ dl. Our results showed that the mean SBP was significantly higher in cases 127.00 ± 14.88 mmHg compared to controls 113.00 ± 6.75 mmHg. Also DBP and MABP were significantly higher in cases than controls; 83.00 ± 8.83 mmHg and 97.66 ± 10.45 mmHg in cases versus 74.00± 5.16 mmHg and 86.98 ± 5.08 mmHg in controls, respectively (p < 0.05). These findings were consistent with previous studies by*Hulter et al.(22)* and *Hanson and Linas (23)* who reached a conclusion that ESRD patients had higher blood pressure.

These results can be explained by the following; acute elevation of PTH is shown to cause vasodilation by inducing endothelial nitric oxide release and smooth muscle relaxation; however, chronic elevation of PTH causes systemic hypertension due to

vasoconstriction related to intracellular calcium accumulation in vascular smooth muscle *(19,22&23)*.This effect may cause hypertension in patients with hyperparathyroidism.

Our results also stated that that levels of both urea and creatinine were much higher in cases compared to controls, for example the mean urea level of the cases group was almost 5 times higher than that of control group, 165.60 ± 34.23 mg / dl in cases and 36.10 ± 5.72 mg / dl in controls ($p < 0.05$). Also, creatinine levels were more than tenfold higher in cases compared to controls ($p < 0.05$). In contrast, albumin levels in cases were significantly lower than the levels of the control group 3.85 ± 0.29 g / dl versus 4.32 ± 0.25 g / dl ($p < 0.05$). Such findings are in line with many previous results and the basic knowledge which suppose much worse renal function for ESRD patients compared to their controls *(24)*. This study also showed that calcium levels were significantly lower among cases ($p < 0.05$). Besides, corrected calcium levels were also lower amongst cases but these differences were statistically insignificant ($p > 0.05$). The table also shows that phosphorus levels were higher in cases 6.03 ± 1.38 mg / dl than controls 3.64 ± 0.31 mg / dl ($p < 0.05$). Unlike calcium and corrected calcium, calcium product was much higher in cases in comparison to controls ($p < 0.05$). Besides, PTH levels recorded very high figures in cases in comparison to controls; 407.42 ± 306.60 pg / dl in cases and 22.28± 3.10 pg / dl in controls ($p < 0.05$).

In our study, the genotypes of cases were distributed as following, 22.5% for bb , 50.0% for Bb and 27.5% for BB compared to 4.0% for bb , 58.0% for Bb and 38.0% for BB in controls. Similarly, a study conducted by *Zhang et al. (25)* on patients with CKD on dialysis, showed domination of Bb genotype among patients (77%). *Moreover, El-Gawad et al. (26)* results were in line with both our results and Olynka's work were the apportionment frequencies of bb, Bb, BB and genotypes in the control group were 23.3, 50, and 26.7 %; respectively. *Kaleta et al (27)* showed that the genotype in polish population distribution between the control groups was as follows; 17, 42 and 41%, respectively for the BB, Bb and bb genotype. This variation may be referred to as racial variability in the studied populations. It is worth noting that, in the current study, carriers of the homozygous *bb* genotype were significantly higher among patients than controls (p=0.01).

In the study by, *Barreto and colleagues (18)* they concluded that, secondary hyperparathyroidism is a popular appearance in patients with chronic kidney failure and is differentiated by increasing serum parathyroid hormone and parathyroid hyperplasia, and also, imbalances in calcium and phosphorus metabolism.*Jiang et al. (19*) justified these findings by the inhibitory role played by VDR on calcium-sensing receptors expressed in parathyroid glands. The authors suggested that calcium-sensing receptors, lead to further greater in the release of PTH and as a result secondary hyperparathyroidism. In a trial to reveal the relation between VDR *(BsmI)* polymorphism and PTH levels, patients carrying the BB genotype had the lowest PTH level (401.87±269.19) pg\ml, yet it didn't reach significant difference (p=0.997). These results were in agreement with Olynka al. () who reported that Patients who were homozygous for allele B had lower serum PTH concentrations (p=<0.001).

We further divided patients according to PTH levels, > 300 and < 300pg/ml; the apportionment frequencies of the different genotypes among patients showed no significant difference in the distribution of VDR polymorphism between both groups ($p > 0.05$).These findings are in line with *Ozdemir et al. (28)*who reported that no connection among secondary hyperparathyroidism and VDR various in ESRD patients. Also, *Fernandez et al (29)* observed that the BB genotype and B allele were considerably much frequent in Spanish patients with the end-stage kidney failure with few PTH levels than in patients with great PTH levels (32.3% versus 12.5% and 58.8% versus 39.1%; respectively).

In addition, *Tagliabue et al (30)* showed a greater frequency of BB different between Italian dialysis patients with hypoparathyroidism than patients with secondary hyperparathyroidism (34% versus 16%). Moreover, the preventive influence of the B allele has been illustrated in Japanese patients undergoing hemodialysis. *Valdivielso and Fernandez (20)* designed greater research minimizing the effect of the time on hemodialysis as a significant danger agent for the evaluation of sHPT. Moreover, they showed a greater appearance of the B allele in the group of patients with less PTH levels. Therefore, it is very difficult to evaluate the highest in the danger of improving sHPT connected with having a specific BsmI genotype. Meanwhile, almost all the statements published point out that there is some effect of BsmI genotype on the sHPT progress. To protect sHPT in early stages of CRF, the utilize of BsmI polymorphism to determine the danger of the patients to improve sHPT could be an option.

In this situation, all the statements published so far confirmed in the connection of the bb genotype with greater PTH levels through the connection of BsmI genotype with PTH levels were also tested after renal transplantation *(26,31&32).*

In summary, a vast amount of information has been collected through the years regarding the association of VDR polymorphisms with susceptibility to suffer different diseases. Unfortunately, much less studies tried to link between these VDR polymorphisms and ESRD. Also, the outcomes obtained consequently are conflictive, and the function of VDR polymorphisms remains unknown. It is clear that the effect of the polymorphisms could not be concerning to alterations in the protein structure but to variations instability and/or translation effectiveness of the RNA, or even to alterations in a totally various gene. In this final situation, the VDR polymorphisms would be done as a marker of truthful roles polymorphisms other places. It is also possible that variations in race, the diet may change the effect of the polymorphisms on the susceptibility to diseases, diluting the impacts noticed in other populations.

Conclusion

The shortage of comprehension of the cellular and molecular processes affected by the polymorphisms produces the surveillance studies very difficult to explain. Consequently the utilization of VDR polymorphisms as diagnostic tools, or even as markers for a greater propensity to experience some diseases, is still a matter of debate. Moreover, potential should be placed in the comprehension of the molecular and cellular differences influenced by the polymorphisms and in carrying out observational

studies in bigger populations. In this research, especially is noticed may be paid to the impacts of environmental contributions for the best comprehension of the function of VDR polymorphisms.

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