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Vitamin D receptor gene polymorphism in Madura pregnant women with hypertension: a case control study

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Abstract

Background: Genetic factors are important considerations in the etiology of preeclampsia and gestational hypertension. Several previous studies have shown an association of Vitamin D receptor (*VDR*) gene polymorphisms with hypertension in pregnancy. However, the number of studies is still very limited and the results differ from one another.

Aim of the study: This study aimed to analyze the polymorphisms of rs2228570 and rs731236 of the *VDR* gene in subjects with hypertension and non-hypertension in pregnancy in Madura ethnicity.

Subjects and methods: The researchers conducted tests for two polymorphisms in the *VDR* gene among 210 subjects consisting of 105 pregnant women with hypertension and 105 non-hypertension pregnant women from Madura ethnicity. The rs2228570 (T>C) and rs731236 (C>T) polymorphisms were detected by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism. All data were analyzed by T-tests and Chi-Square tests.

Results: The TT genotype frequency of rs2228570 (15.2%) in the hypertension group was higher than in the control group (6.7%) ($p = 0.047$). Subjects with the TT genotype at rs2228570 showed a 3.048 times greater risk of developing hypertension than the CC genotype (OR = 3.048: 1.135–8.183, $p = 0.023$). The T allele frequency of rs2228570 (40.5%) in the hypertension group was higher than in the control group (30.5%) ($p = 0.032$). Subjects with the T allele had 1.551 times greater risk of developing hypertension. There was no significant difference in genotype and allele of rs731236 between hypertension subjects and controls.

Conclusion: The TT genotype and T allele of rs2228570 in the hypertension group were risk factors for hypertension in this study. While the TT genotype and T allele at rs731236 were not risk factors for hypertension in pregnancy. Genotyping of *VDR* gene polymorphisms in pregnant women is expected to be useful in strategies for treating hypertension in pregnancy.

Keywords: Vitamin D receptor, Polymorphism, Pregnant women, Hypertension in pregnancy

Background

Hypertension in pregnancy is an important cause of severe morbidity, long-term disability and maternal and infant mortality. In Africa and Asia, nearly one-tenth of all maternal deaths are related to hypertensive disorders of pregnancy [1]. In Indonesia, hypertension is one of the five maincauses of maternal death. It was recorded that from 2010 to 2013 the proportion of maternal deaths due to hypertension increased from 21.5 to 27.1% [2].

Genetic factors are important considerations in the etiology of preeclampsia and gestational hypertension. A meta-analysis examining genetic associations in preeclampsia identified 22 genetic variants, 7 of which were significantly associated with preeclampsia. These variants reside in or near the genes: Angiotensin Converting

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Enzyme (ACE), Cytotoxic T-Lymphocyte-Associated Antigen-4 (CTLA4), Coagulation Factor II (F2), Coagulation Factor V (FV), Lipoprotein Lipase (LPL) and Serpin Family. E Member 1 (SERPINE1) [3]. Several studies have also shown an association of VDR gene polymorphisms with hypertension in pregnancy [4–8]. In addition, there are several studies examining the VDR gene polymorphism in subjects (non-pregnant women) with hypertension and the results show a relationship between BsmI and FokI polymorphisms in the VDR gene with the risk of essential hypertension [9–11].

Studies on the relationship of the VDR gene with hypertension in pregnancy are still very limited and the results differ from one another. Studies in Brazil [4] and Italy [8] showed no significant difference in the VDR gene rs2228570 polymorphism between the hypertension subjects and the control group. In contrast, studies in China [5] and Iran [6, 7] found a significant difference in the rs2228570 polymorphism of the VDR gene between the hypertension and control groups. The rs2228570 polymorphism shows a T-C transition (ATG-ACG) in exon II of chromosome 12 [12]. Mutation of ATG (methionine) to ACG (threonine) causes a change in the start codon so that the next amino acid cannot be encoded [13]. Another polymorphism, the rs731236 polymorphism of the VDR gene, shows a C-T transition (ATC-ATT) in exon IX of chromosome 12 [12]. Both ATC and ATT encode isoleucine, and these mutations are called silent mutations [13].

In this study, the researchers conducted testson subjects with hypertension and non-hypertension with Madura ethnicity. The Madura are one of the major ethnic groups in Indonesia. This ethnic group comes from East Java Province. The spread of this ethnicity to other regions in Indonesia and abroad occurred quickly due to their habit of wandering [14]. The description of the health of pregnant women in East Java Province itself shows a high maternal mortality rate of 89.81 per 100,000 live births with the highest cause being preeclampsia/eclampsia (31.15%) [15]. Based on this background, the researchers conducted a study with the aim of analyzing the rs2228570 (T>C) and rs731236 (C>T) polymorphisms of the VDR gene in subjects with hypertension and non-hypertension with Madura ethnicity.

Methods

Subjects

All participants were of Madura descent. Subjects were divided into two groups, case group with hypertension and control group with non-hypertension. The similarity of risk factors for preeclampsia and gestational hypertension was the reason for the study did not classify hypertension in pregnancy. The subjects included 210 unrelated volunteers: 105 pregnant women with hypertension and 105 control. The sample size was calculated using the Lemeshow formula with $\alpha = 0.05$, power of the test = 0.8 and the values of $P1 = 0.3$ and $P2 = 0.488$. The proportion value is obtained from previous studies [16]. Subjects with chronic hypertension, multiple pregnancies, renal impairment, and parathyroid hormone disorders were excluded.

Subjects characteristic

Body mass index (BMI = weight in kg divided by height in m^2), blood pressure (systolic and diastolic in mmHg) were measured with a standardized and calibrated scale. Hypertension category was determined if Systolic Blood Pressure (SBP) $\geq$ 140 mmHg and Diastolic Blood Pressure (DBP) $\geq$ 90 mmHg.

VDR gene genotyping

Venous blood samples were drawn. The puffy coat layer was collected for Deoxyribonuleic Acid (DNA) extraction. For genotype analysis, DNA was extracted from leukocytes with a Genomic DNA Mini Kit according to the manufacturer's protocol (Applied Geneaid). Genotyping was performed using the following primer sequences (Applied LIGO): rs2228570; forward, 5′-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3′; reserve, 5'-ATG GAA ACA CCT TGC TTC TTC TCC CTC-3′; and for rs731236; forward, 5′- CAG AGC ATG GAC AGG GAG CAA-3′; and reverse, 5′-GCA ACT CCT CAT GGC TGA GGT CTC-3′ [17, 18]. The conditions for polymerase chain reaction (PCR) were: rs228570; 95 °C for 1 min, 95 °C for 15 s, 58 °C for 15s, 72 °C for 10s for 35 cycles, and extra extension at 72 °C for 5 min, rs731236; 95 °C for 1 min, 95 °C for 15 s, 63 °C for 15s, 72 °C for 10s for 35 cycles, and extra extension at 72 °C for 5 min [19]. The PCR results were 265 bp for rs2228570 and 740 bp for rs731236. Polymorphism was determined by digestion of PCR products using FokI and TaqI enzymes (New England Biolabs Inc.) for rs2228570 (R0109S) and for rs731236 (R0149S), respectively. Gel electrophoresis with 2% agarose was performed to analyze the digestion. The digested products for rs2228570 were 265 bp for the C allele and 169 and 96 bp for T allele (Fig. 1). The digested products for rs731236 were 495 and 245 bp for C allele and 290, 245 and 205 bp for T allele (Fig. 2).

Data analysis

Independent Sample *T*-tests was doneto match the age, BMI and blood pressure of each group. Genotype distributions were examined for Hardy-Weinberg equilibrium (HWE), and single nucleotide polymorphisms (SNPs) of rs2228570 and rs731236 *VDR* gene for the hypertension and control groups were compared using chi-square

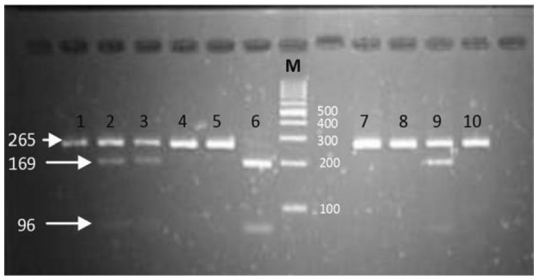

Fig. 1 Digestion product of rs2228570 with Fok1 enzyme, lane 1, 4, 5, 7, 8 and 10 = CC, lane 2, 3 and 9 = CT, lane 6 = TT M = marker

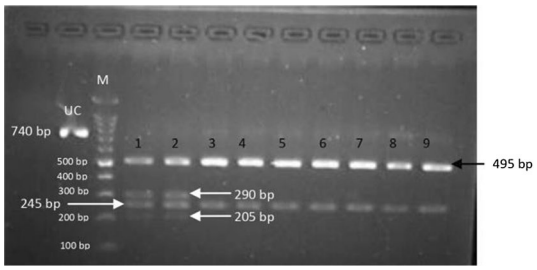

Fig. 2 Digestion products of rs731236 with Taq1 enzyme, lane 1 and 2 = CT, lane 3, 4, 5, 6, 7, 8 and 9 = CC, M = markers, UC = uncut

Table 1 Characteristics of subjects in the hypertension in pregnancy and control groups

	Hypertension	Control	*P*[#]
N	105	105	
Age (year)	29.10 ± 6.90	27.07 ± 6.03	0.024*
BMI	24.48 ± 4.00	22.27 ± 3.14	< 0.001*
Systolic BP (mmHg)	158.29 ± 17.40	106.67 ± 8.62	< 0.001*
Diastolic BP (mmHg)	100.19 ± 6.35	71.43 ± 6.85	< 0.001*

BMI = body mass index; BP = blood pressure

[#] Analyzed with t-test

*Statistically significant

analysis. All of the tests were performed using Statistical Package for the Social Sciences (SPSS) version 16 (IBM Corp., Armonk, NY). Statistical significance was defined at $P < 0.05$.

Results

The characteristic of all subjects are shown in Table 1. The mean of age, BMI, systolic and diastolic blood pressure in the hypertension group were higher than in the control group ($P < 0.05$). There was a difference in age and BMI between the two groups. Both of these factors are risk factors for hypertension in pregnancy. Maternal age > 35 years and high BMI are at risk of increasing the occurrence of hypertension in pregnancy [20].

Table 2 Genotype frequency of rs2228570 and rs731236 in the case and control groups

Model	Hypertension (n = 105)	Control (n = 105)	OR (95% CI)	*P*
rs222857				
Codominant				
CC	36 (34.3)	48 (45.7)	1 (ref)	
CT	53 (50.5)	50 (47.6)	1.413 (0.792–2.523)	0.242
TT (*wild type*)	16 (15.2)	7 (6.7)	3.048 (1.135–8.183)	0.023
Dominant				
CC	36 (34.3)	48 (45.7)	1 (ref)	
CT + TT	69 (65.7)	57 (54.3)	1.614 (0.925–2.816)	0.091
Recessive				
CC + CT	89 (84.8)	98 (93.9)	1 (ref)	
TT	16 (15.2)	7 (6.7)	2.517 (0.990–6.401)	0.047
Allele				
C	125 (59.5)	146 (69.5)	1 (ref)	
T	85 (40.5)	64 (30.5)	1.551 (1.037–2.321)	0.032
rs731236				
Codominant				
TT (*wild type*)	98 (93.3)	97 (92.4)	1 (ref)	
TC	7 (6.7)	8 (7.6)	0.866 (0.302–2.481)	0.789
Allele				
T	203 (96.7)	202 (96.2)		
C	7 (3.3)	8 (3.8)	0.871 (0.310–2.446)	0.793

CI = confidence interval, OR = odds ratio

Genotype frequency of rs2228570 and rs731236 in the hypertension and control groups areshown in Table 2.

Significant differences were found in the TT genotype rs2228570 between hypertensive subjects and controls. Subjects with theTT genotype also showed 3048 times greater risk of developing hypertension in pregnancy than the CC genotype. In the recessive model, subjects with the TT genotype showed 2517 times greater risk of developing hypertension in pregnancy than CC and CT. The results of the analysis indicated that the distribution of alleles was significantly different between the two groups. The T allele in hypertensive subjects showed a greater frequency than in control subjects. The subjects with the T allele had1551 times greater risk of developing hypertension in pregnancy.

Based on data analysis, it was found that there was no significant difference for rs731236 between hypertensive

subjects and controls. The CC genotype was not found in this study. The results of the analysis indicatedthat the distribution of alleles was not significantly different between the two groups. The T allele in both groups showed a greater frequency than the C allele. The results of the analysis showed a low odds value (less than 1) in this polymorphism.

Table 3 shows several studies of the rs2228570 and rs731236 polymorphisms that have been conducted in populations in Brazil, Han (China), Kurdish (West Iran), Iran, Italy and (Madura) Indonesia.

Discussion

Studies that analyze the rs2228570 (FokI) and rs731236 (TaqI) *VDR* gene polymorphisms in gestational hypertension have not been widely done. Currently, studies that have been conducted and published are on the population in Brazil [4], the Han population in China [5], the Kurdish population in Western Iran [6], and the populations in Iran [7] and in Italy [8]. Meanwhile, this study analyzed the *VDR* Fok1 and Taq1 gene polymorphisms in the Madura ethnic group in Indonesia.

The study in Madura subjects showed that the frequency of the C allele at rs2228570 was higher than that of the T allele in both groups and showed a significant difference. These results are in line with studies in China (Han) [5] and Iran [6, 7]. However, in contrast to studies in populations in Brazil [4] and Italy [8] where the frequency of the C allele was higher than that of the T allele, there was no significant difference.

The results showed that subjects with the wild type TT genotype had 3048 times greater risk and those with the T allele had1,551 times greater risk of developing hypertension in pregnancy. The results of this study differ from the results of studies in China and Western Iran which showed that the C allele increased the risk of preeclampsia. However, the findings in this study are consistent with the results of a study of male hypertension in the Han Chinese population which stated that the Fok1 *VDR* gene polymorphism was associated with a reduced risk of hypertension [21].

To date, the FokI polymorphism is the only known functional polymorphism in the *VDR* gene [22]. SNPs of FokI (rs2228570) are variations of the base T to C at the translation initiation codon (ATG) in exon 2 [23, 24]. This polymorphism is also known as an initial codon polymorphism. These variations lead to shorter protein synthesis with increased biological activity [25]. This mechanism may occur and influence the reduction of hypertension risk. However, the reason for the difference

Table 3 The frequency of VDR gene among different ethnicities

Ethnicity (area)	Research individuals	Genotypes			Total *n*	*P*
		CC (%)	CT (%)	TT (%)		
rs2228570						
Brazil [4]	GH	55 (36)	79 (51)	20 (13)	154	> 0.05
	Preeclampsia	66 (41)	66 (41)	30 (18)	162	
	Normal	90 (42)	104 (49)	19 (9)	213	
Han (China) [5]	Preeclampsia	163 (40)	176 (44)	63 (16)	402	0.001
	Normal	161 (29)	292 (53)	101 (18)	554	
Kurdish (West Iran) [6]	Preeclampsia	72 (72)	22 (22)	6 (6)	100	0.011
	Normal	55 (55)	38 (38)	7 (7)	100	
Iran [7]	Preeclampsia	106 (70)	38 (22)	8 (8)	152	0.02
	Normal	89 (55)	54 (32)	17 (12)	160	
Italia [8]	GH	55 (47)	43 (37)	18 (16)	116	> 0.05
	Normal	31 (45)	27 (39)	11 (16)	69	
Madura (Indonesia)	GH	36 (34)	53 (51)	16 (15)	105	0.023
	Normal	48 (46)	50 (47)	7 (7)	105	
rs731236						
Kurdish (West Iran) [6]	Preeclampsia	40 (40)	51 (51)	9 (9)	100	0.8
	Normal	40 (40)	55 (55)	5 (5)	100	
Iran [7]	Preeclampsia	59 (39)	71 (47)	22 (14)	152	0.7
	Normal	65 (41)	70 (44)	25 (15)	160	
Madura (Indonesia)	GH	98 (93)	7 (7)	0 (0)	105	0.8
	Normal	97 (92)	8 (8)	0 (0)	105	

GH = gestational hypertention

in activity between the two proteins, whether due to differences in the ability to bind 1,25-dihydroxy vitamin D3 or to activate transcription, requires further studies [17].

Another study showed that 1,25(OH)2D3 drastically reduced renin mRNA expression in As4.1 cells or was stably transfected by *VDR* cDNA. To elucidate the molecular mechanism by which1,25(OH)2D3 suppresses renin gene expression, transfected cells were used to analyze the renin gene promoter by luciferase reporter assay. When the cells were transfected with a luciferase reporter plasma containing a 4.1 kb 5′flanking sequence of murine *Ren-1c* gene, 1,25(OH)2D3 treatment markedly reduced promoter activity [26]. This finding confirmed that 1,25(OH)2D3 directly and negatively regulates renin gene transcription mediated by the *VDR* mechanism. However, the role of *VDR* in pregnancy problems has not been fully elucidated [27].

In this study, no CC genotype was found for the SNPs Taq1/rs731236 (0.0%). Variations in the frequency of polymorphisms depend on ethnic background [19]. As a comparison in other studies, it was shown that the frequency of the CC genotype varied greatly, namely 6.5% in Kurdish [6], 1.4% in Japanese and 16.0% in Caucasian [28], and 0.0% in Chinese populations [29].

The study results showed that there were no significant differences in Taq1 SNPs in the two groups. These results are in line with previous studies where the Taq1 genotype and allele did not show significant differences [6, 7]. The Taq1 *VDR* gene is located at 3' UTR and is thought to be involved in the regulation of gene expression, especially mRNA stability [18]. The substitution of ATT into ATC is a synonymous change at codon 352 (isoleucine) in exon IX and is a silent mutation [30]. Therefore, the TaqI polymorphism does not seem to have a direct effect on *VDR* function.

This research is the first study to examine the rs2228570 polymorphism of the *VDR* gene to reduce the risk of hypertension in pregnancy in ethnic Madurese, and this is probably the first study conducted in Indonesia. The weakness of this study is that the sample size was small and the subjects involved were only Madura, so they are not representative for other ethnicities. Therefore, further studies need to involve other ethnic groups in Indonesia and a larger sample size to confirm the results of this study.

Conclusions

The frequency of the TT genotype and T allele of rs2228570 in the hypertensive group in pregnancy were higher than in controls and were risk factors in this study. While the TT genotype and T allele at rs731236 were not risk factors for hypertension in pregnancy.

This study can form the basis for replication studies in a larger population. Furthergenotyping of *VDR* gene polymorphisms in pregnant women is expected to be useful in strategies for treating hypertension in pregnancy.

Abbreviations

BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; DBP: Diastolic blood pressure; DNA: Deoxyribonucleic acid; GH: Gestational hypertention; HWE: Hardy Weinberg equilibrium; OR: Odds ratio; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; SBP: Systolic Blood Pressure; SNPs: Single nucleotide polymorphisms; SPSS: Statistical Package for the Social Sciences; VDR: Vitamin D receptor.

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Authors' contributions

DS performed the study, analyzed and interpreted the subject data and drafted the initial manuscript. PH and DSN conceptualized and designed the study. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author [DS]. The data are not publicly available due to them containing information that could compromise research participant privacy/consent.

Declarations

Ethics approval and consent to participate

The study was approved by the Medical and Health Research Ethics Committee Faculty of the Medicine, Public Health and Nursing, Universitas Gadjah Mada (Ref: KE/FK/0423/EC/2018). Written informed consent was obtained from all participants for this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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