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Vitamin D Receptor Gene Polymorphism in Madurese Pregnant Women with Hypertension : A Case Control Study

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Vitamin D Receptor Gene Polymorphism in Madurese Pregnant Women with Hypertension : A Case Control Study

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Abstract

Background : Genetic factors are important factors 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. Therefore, researchers conducted a study with the aim of analyzing the polymorphisms of rs2228570 and rs731236 of the VDR gene in subjects with hypertension in pregnancy and non-hypertension in pregnancy in Madura ethnicity.

Methods : Researchers tested two polymorphisms in the VDR gene on 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 PCR-RFLP. All data were statistically analyzed by T-Test and Chi-Square.

Results : The TT genotype frequency of rs2228570 (15.2%) in hypertension group was higher than in non-hypertension group (6.7%) (p = 0.047). The T allele frequency of rs2228570 (40.5%) in the hypertension group was higher than in the non-hypertension group (30.5%) (p = 0.032). 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 confer 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 frequency of the TT genotype and T allele of rs2228570 in the hypertension group was a risk factor for hypertension in this study. At rs731236 there was no significant difference in TT genotype and T allele between hypertension subjects and controls. 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

1. 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 biggest causes 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 factors 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 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 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 (treonine) 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 both encode isoleucine, and these mutations are called silent mutations [13].

And in this study, researchers conducted a study on subjects with hypertension and non-hypertension on 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 the habit of wandering [14]. The description of the health of pregnant women in East Java Province itself shows a maternal mortality rate of 89.81 per 100000 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 in Madura ethnicity.

2. Methods

2.1. Subjects

All participants were of Madura descent. 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] .

2.2. Subjects Characteristic

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 if systolic blood pressure (SBP) ≥ 140 mmHg and dyastolic blood pressure (DBP) ≥ 90 mmHg.

2.3. VDR gene genotyping

Venous blood samples were drawn. The puffy coat layer was collected for 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 condition for PCR were: rs228570; 95 ºC for 1 min, 95 ºC for 15 s, 58 ºC for 15s, 72 ºC for 10s for 35 cycles, and extra extension at 72 ºC for 5 min, rs731236; 95 ºC for 1 min, 95 ºC for 15 s, 63 ºC for 15s, 72 ºC for 10s for 35 cycles, and extra extension at 72 ºC for 5 min [19]. The PCR results were 265 bp for rs2228570 and 740 bp for rs731236. Polymorphism was determined by digestion of PCR product 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 product for rs2228570 was 265 bp for the C alel and 169 and 96 bp for T alel. The digested product for rs 731236 was 495 and 245 bp for C alel and 290, 245 and 205 bp for T alel.

2.4. Data analysis

Independent Sample T Test was performed to match the age, BMI and blood pressure and of each group. Genotype distributions were examined for Hardy-Weinberg equilibrium (HWE), and SNPs of rs2228570 and rs731236 VDR gene for the hypertension and control groups were compared using chi-square analysis. All of the tests were performed using SPSS version 16. Statistical significance was defined at $P < 0.05$.

3. Result

The characteristic of all subjects were 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 ($P < 0.05$).

Table 1. Characteristic 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
[#] Analyzed with t-test
[*] Statistically significant

The genotype distribution of rs2228570 and rs731236 followed Hardy Weinberg Equilibrium as shown in Table 2.

Table 2. The measurement of Hardy Weinberg equilibrium among the cases and controls

	Chi-square	P value
rs228570	1.07	0.3009
rs731236	0.29	0.5902

Genotype frequency of rs2228570 an rs731236 in the hypertension and control groups is shown in Table 3.

Table 3. Genotype frequency of rs2228570 and rs731236 in the case and control groups

Model	Hypertension (n=105)	Control (n=105)	OR (CI 95%)	P

rs222857				
Codominant[a]				
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[a]				
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[a]				
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
Allel[a]				
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[a]				
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
Allel[a]				
T	203 (96.7)	202 (96.2)		
C	7 (3.3)	8 (3.8)	0.871 (0.310-2.446)	0.793

Significant differences were found in the TT genotype rs2228570 between hypertensive subjects and controls. The TT genotype also showed a 3,048 times greater risk of developing hypertension in pregnancy than the CC genotype. In the recessive model, the TT genotype showed a 2,517 times greater risk of developing hypertension in pregnancy than CC and CT. The results of the analysis showed 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 T allele confer 1,551 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 showed that 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 4 shows several studies of the rs2228570 and rs731236 polymorphisms that have been carried out in populations in Brazil, Han (China), Kurdish (West Iran), Iran, Italy and (Madura) Indonesia.

Table 4. The frequency of VDR gene among different ethnicities

Ethnicity (area)	Research individuals	Genotypes			Total n	P
rs2228570		CC (%)	CT (%)	TT (%)		
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 (Iran Barat) [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		TT (%)	TC (%)	CC (%)		
Kurdish (Iran Barat) [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	

4. Discussion

Studies that analyze the rs2228570 (FokI) and rs731236 (TaqI) VDR gene polymorphisms in gestational hypertension have not been widely carried out. 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], the population in Iran [7] and in Italy [8]. Meanwhile, this study analyzed the VDR Fok1 and Taq1 gene polymorphisms in the Madura in Indonesia.

The study in Madura 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 a 3,048 times greater risk and the T allele gave 1,551 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 PE. 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 [20].

To date, the FokI polymorphism is the only known functional polymorphism in the VDR gene [21]. SNPs FokI (rs2228570) are variations of the base T to C at the translation initiation codon (ATG) in exon 2 [22-23]. This polymorphism is also known as initial codon polymorphism. These variations lead to shorter protein synthesis with increased biological activity [24]. This mechanism may occur and influence the reduction of hypertension risk. However, the reason for the difference in activity between the two proteins, whether due to differences in the ability to bind 1,25-dihydroxy vitamin D3 or to activate transcription, remains to be studied further [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 that 1,25(OH)2D3 suppresses renin gene expression, transfected cells were used to analyze the renin gene promoter by luciferase reporter assay. When cells were transfected with luciferase reporter plasma containing 4.1 kb 5'flanking sequence murine Ren-1c gene, 1,25(OH)2D3 treatment markedly reduced promoter activity [25]. This 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 [26].

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 [27], and 0.0% in Chinese [28].

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 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 [29]. Therefore the TaqI polymorphism does not seem to have a direct effect on VDR function.

This study 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 is small and the subjects involved are only Madura, so they are not representative for other ethnicities.

Therefore, further studies need to involve other ethnic groups in Indonesia and in a larger sample size to confirm the results of this study.

5. Conclusion

The frequency of the TT genotype and T allele of rs2228570 in the hypertensive group in pregnancy was higher than in controls and was a risk factor in this study. At rs731236 there was no significant difference in TT genotype and T allele.

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

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable

Availability of data and material

The genotyping results of subjects recruited for this study is available in the manuscript.

Competing interest

The authors declare no competing interests.

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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 and approved the final manuscript.

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