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Association of Leu432Val (rs1056836) polymorphism of the *CYP1B1* gene with lipid profile in hypertensive Slovak women

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Abstract: Leu432Val (rs1056836) polymorphism of the *CYP1B1* gene was examined in relationship with lipid profile in hypertensive Slovak women according to their menopausal status. The entire study sample comprised 255 women suffering from hypertension aged from 39 to 65 years who were recruited from different localities in the western, southern, and middle parts of Slovakia. The participants provided a saliva or blood sample for DNA genotyping and a blood sample for biochemical analysis. The Leu432Val genotypes demonstrated statistically significant associations with all monitored atherogenic indices – total cholesterol-to-HDL-Cholesterol (AI1), Non-HDL-Cholesterol (AI2), LDL-Cholesterol-to-HDL-Cholesterol (AI3), and the logarithm of the ratio of plasma concentration of triglycerides to HDL-cholesterol (AIP log) in hypertensive pre/perimenopausal women. The mean values were significantly lower in women carrying the Val/Val genotype. In early postmenopausal hypertensive women the Leu432Val genotypes were statistically significant and associated with LDL-cholesterol (LDL-C) and AI2. The mean values of LDL-C and AI2 were significantly lower in women carrying the Leu/Leu genotype. In conclusion, the Leu432Val polymorphism may be associated with the atherogenic indices and LDL-C in hypertensive women.

Key words: hypertension, Leu432Val polymorphism, menopausal status, lipids

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Introduction

Cardiovascular disease (CVD) has the highest mortality rate in the world. The incidence of CVD is related to gender, and premenopausal women have a lower incidence of hypertension, atherosclerosis, myocardial dysfunction, ventricular hypertrophy, heart failure, and myocardial ischemia than age-matched men (Kander et al. 2017; Somani et al. 2019). Following menopause and loss of endogenous estradiol (major ovarian estrogen), these gender-based differences narrow (Patel et al. 2018). This fact suggests that estradiol protects the cardiovascular system. Estradiol induces vasoprotective effects by multiple mechanisms, including alterations in plasma concentrations of lipoproteins (decrease in low-density lipoprotein cholesterol (LDL-C) levels, decrease in oxidized LDL formation, increase in high-density lipoprotein cholesterol levels (HDL-C)), hemostatic factors, glucose, and insulin (Dubey and Jackson 2001). Estrogen deficiency after menopause is the main reason for deterioration of the serum lipid profiles (Rexrode et al. 2003; Fonseca et al. 2017).

This finding suggests that, hormonal interplay with lipid metabolism could have a significant role to play in modulating CVD risk (Dubey et al. 2005; Mc Auley and Mooney 2014). Individual genetic variability of estradiol metabolism has been described as a significant contributor to the hormone-dependent disorder susceptibility with variations depending on ethnic background. Among others, the variations of many genes encoding the cytochrome P450 (CYP) superfamily of enzymes, including variations in the *CYP1B1* gene, are considered to play an important role in this regard (Huber, Schneeberger and Tempfer 2002). The human *CYP1B1* gene has been mapped to chromosome 2 and encompasses three exons. The mRNA is 5.2 kilobases and encodes a protein of 543 amino acids (Faiq et al. 2014). Several genetic polymorphisms have been identified in the *CYP1B1* gene, and one of them, the Leu432Val polymorphism, (rs1056836; 4326C > G), located in a catalytically important heme-binding domain in exon 3 results in altered *CYP1B1* enzyme activity (Shimada et al. 1999). The *CYP1B1* 432Val allele encodes an enzyme with higher activity to 17ß-estradiol than the 432Leu variants (Tang et al. 2000). In recent years, multiple lines of evidence from both humans and mice have shown a significant role for *CYP1B1* enzyme in the cardiovascular system (Conway et al. 2009; Kaur-Knudsen et al. 2009; Song et al. 2016; Li et al. 2017; Mikstacka and Dutkiewicz 2021), development of hypertension and associated pathophysiological changes (Malik et al. 2012; White et al. 2012; Shah et al. 2019). Also, *CYP1B1* polymorphisms were associated with different types of cancers: Endometrial (Sliwinski et al. 2010; Zhang et al. 2021), breast (Matyjasik et al. 2007; Almeida et al. 2021; Martínez-Ramírez et al. 2021) and colorectal cancer (Hlavata et al. 2010; Trubicka et al. 2010). The *CYP1B1* Leu432Val polymorphism was also found to be significantly associated with the effect of hormone therapy on bone mineral density and LDL-C in postmenopausal Japanese women (Jinhua et al. 2009). In our previous pilot study (Luptakova et al. 2012), *CYP1B1* Leu432Val polymorphism appeared to modify the plasma levels of triglycerides (TG), the values of the atherogenic indices: TC-to-HDL-C ratio, and log(TG-to-HDL-C) ratio in Slovak women in their reproductive period. The mean values

were significantly lower in women carrying the Val/Val genotype.

In this cross-sectional study, we attempted to clarify the association between *CYP1B1* Leu/Val polymorphism and differences in serum lipid profile (TG, TC, LDL-C, HDL-C, atherogenic indices) and another biochemical variables in Slovak midlife women with essential hypertension in pre-/perimenopausal and early postmenopausal period of life.

Subjects and methods

This study was based on data collected during a cross-sectional survey in Slovakia to analyze the effect of genetic variants of some candidate genes on health biomarkers in Slovak women. The investigated sample comprised 255 sample of midlife women suffering from hypertension of European origin aged from 39 to 65 years, who were recruited from different localities in the western, southern, and middle parts of Slovakia. All participants were interviewed during a medical examination in the morning and were investigated with respect to their medical, anthropometric and lifestyle factors at local Health Centres. Women were approached and recruited using a non-random procedure based on volunteering and convenience. Each woman provided written informed consent for this study which adhered to the Declaration of Helsinki principles. Those who were unable to give a response due to serious physical or mental illness and with whom anthropometry and blood measurements could not be performed were excluded from the study. Data concerning lifestyle habits including physical activity, smoking, health status and menstrual cycle characteristics were investigated via a questionnaire. Women recovering from acute disorders such as cancer, myocardial infarction or stroke were also excluded from the survey. Women were divided according to their menopausal status into pre-, peri- and postmenopausal groups. Due to the low number of perimenopausal women, this group was amalgamated with premenopausal women.

Biochemical analysis

Biochemical levels of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (TG) were analyzed from fasting plasma samples by routine laboratory methods in the Department of Clinical Laboratories of the Bratislava Alpha Medical. Low-density lipoprotein cholesterol was calculated from the total cholesterol, HDL-C, and triglyceride values by the Friedewald equation if triglycerides were 4.5 mmol/L. If the serum triglyceride concentration was above this limit, LDL-C was treated as absent. The atherogenic indices were calculated as follows: AI1 = TC (mmol/l) / HDL-C (mmol/l), AI2 (non-HDL-C) = TC (mmol/l) – HDL-C (mmol/l) and AI3 = LDL-C (mmol/l) / HDL-C (mmol/l). Atherogenic index of plasma (AIP) was calculated as a logarithmically transformed ratio of molar concentrations of TG to HDL-C (mmol/l).

Anthropometric and blood pressure measurements

All anthropometric parameters were measured by professional anthropologists and the same instruments were used on all women. Anthropometric measurements were taken using the standard anthropometric technique. Body height was measured with a Sieber and Hegner anthropometer at the head level with the participant standing barefoot and with feet together, with 0.5 cm accuracy. Body weight was then measured on a personal

balance scale with the participant being barefoot and in underwear, with an accuracy of 0.1 kg. Waist and hip circumferences were measured according to the NHLBI Obesity Education Initiative (2000) and WHO (2008). Body mass index (BMI) was calculated as body weight divided by height squared. Waist-to-hip ratio (WHR) was calculated as the circumference of the waist divided by the circumference of the hips. Waist-to-height ratio (WHtR) was calculated as the circumference of the waist divided by height squared.

Resting systolic and diastolic blood pressures were obtained after a 5-minute rest, with the participant in a semi-recumbent position. Incident hypertension was defined as either by SBP ≥ 140 or DBP ≥ 90 mmHg at follow-up health examinations, a self-report of receiving treatment for high BP, and/or a physician's diagnosis of hypertension during the follow-up period. The women who underwent effective blood pressure lowering treatment were also included in our measurements. Consequently, blood pressure values in our study may have been skewed and lower than before starting the treatment.

Genetic analysis

DNA was extracted from peripheral blood samples, or saliva samples, using the SiMax™ Genomic DNA Extraction Kit; and the *CYP1B1* Leu432Val variant was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using the method previously described by Luptakova et al. (2012).

Data analysis

Statistical analyses were performed using IBM SPSS for Windows (Statistical Package for the Social Science, version 20.0, Chicago, Illinois) and continuous data was expressed as mean ± SD and a two-tailed P value equal to or less than 0.05 was considered significant. Genotype distribution was analyzed using the $\chi 2$ test, and allele frequencies were assessed by the $\chi 2$ test with Yates correction. The goodness of fit evaluated whether the genotypic distribution of the *CYP1B1* Leu432Val variant matched with the Hardy–Weinberg equilibrium in hypertensive women. The normality assumption hypothesis was tested by the one-sample Kolmogorov–Smirnov test. Simple comparison of selected variables between the genotype groups, assuming an additive (AM; Leu/Leu, Leu/Val, Val/Val), dominant (DM; Leu/Val + Val/Val vs. Leu/Leu) and recessive model (RM; Val/Val vs. Leu/Val + Leu/Leu), was analyzed using the One Way ANOVA for data with normal distribution and Kruscal-Wallis Test was used for not normally distributed data.

Results

The study group of women were mostly married (69.80%), and the place of birth in towns (52.16%) prevailed. Additional baseline description such as the anthropometric, life style characteristics and distribution of the studied *CYP1B1* variant in hypertensive women are summarized in Table 1.

The participants were mostly non-smokers (70.20%), did not perform sports activities regularly (87.80%) and gained secondary education level (63.10%). The genotype distribution of the *CYP1B1* Leu432Val polymorphism was 19.30% (n = 45), 59.70% (n = 139), and 21.00% (n = 49) in hypertensive Slovak women for the Leu/Leu, Leu/Val, and Val/Val genotypes. The distribution of genotype frequencies of the polymorphism in the study women deviated from the Hardy–Weinberg equilibrium ($\chi 2 = 8.723$; df = 2; P = 0.003).

Table 1. Baseline characteristics of the study women

Variables	N	Mean		SD
Age, years	255	52.40	±	6.10
Height, cm	255	163.00	±	6.00
Weight, kg	255	79.30	±	16.30
Waist circunference, cm	255	93.09	±	14.47
Hip circumference, cm	255	108.46	±	11.83
BMI, kg/m^2	255	29.50	±	6.10
WHR	255	0.90	±	0.10
WHtR	255	0.60	±	0.10
	N			%
***CYP 1B1* (rs1056836; Leu432Val)**				
Leu/Leu	45			19.30
Leu/Val	139			59.70
Val/Val	49			21.00
Leu	229			0.49
Val	237			0.51
Smoking status				
Smokers	76			29.80
Non-smokers	179			70.20
Regular sport activity				
Yes	39			12.20
No	281			87.80
Menopausal status				
Pre-/perimenopausal	94			36.90
Early postmenopausal	161			63.10
Education				
Basic	52			20.40
Secondary	161			63.10
University	42			16.50

Notes: N, number of participants; SD, standard deviation; BMI, body mass index; WHR, waist to hip ratio; WHtR, waist to height ratio

Table 2 compares the mean values of selected biochemical variables and atherogenic indices according to the *CYP1B1* Leu432Val genotypes in the whole group of women in univariate analysis between the additive, dominant, and recessive models. No statistically significant differences were observed between Leu432Val genotypes and the monitored parameters under the different models.

Table 2. Selected biochemical variables according to the *CYP 1B1 Leu432Val (rs1056836)* genotypes in hypertensive women

	Hypertensive women									*AM*	*DM*	*RM*
	CYP 1B1 Leu/Leu			*CYP 1B1 Leu/Val*			*CYP 1B1 Val/Val*					
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p	p	p
Total cholesterol (TC), (mmol/L)	38	5.21	± 0.99	120	5.44	± 1.04	38	5.57	± 0.93	0.287	0.155	0.312
Triglycerides (TG), (mmol/L)	38	1.61	± 0.74	120	1.60	± 1.31	38	1.59	± 1.02	0.678	0.378	0.825
HDL-cholesterol (HDL-C), (mmol/L)	35	1.43	± 0.33	115	1.41	± 0.43	33	1.50	± 0.31	0.548	0.918	0.277
LDL-cholesterol (LDL-C), (mmol/L)	35	3.08	± 0.94	115	3.41	± 1.03	33	3.53	± 0.85	0.127	0.051	0.318
AI1 (TC/HDL-C)	35	3.80	± 0.93	115	4.10	± 1.18	33	3.96	± 1.25	0.383	0.216	0.747
AI2 (TC-HDL-C)	35	3.80	± 0.93	115	4.02	± 1.03	33	4.13	± 1.09	0.374	0.196	0.410
AI3 (LDL-HDL-C)	35	2.24	± 0.76	115	2.60	± 1.02	33	2.53	± 1.04	0.175	0.066	0.933
AIP log (TG/HDL-C)	35	0.01	± 0.25	115	-0.01	± 0.32	33	-0.04	± 0.31	0.789	0.639	0.549

Note: N, number of participants; SD, standard deviation; AI, Atherogenic index; p, value of statistical significance; AM, aditive model (Leu/Leu, Leu/Val, Val/Val); DM, dominant model (Leu/Val + Val/Val vs. Leu/Leu); RM, recesive model (Val/Val vs. Leu/Val + Leu/Leu)

Table 3. Selected biochemical variables according to the *CYP 1B1 Leu432Val (rs1056836)* genotypes and menopausal status in hypertensive women

Pre/perimenopausal status	**Hypertensive women**									*AM*	*DM*	*RM*
	CYP 1B1 Leu/Leu			*CYP 1B1 Leu/Val*			*CYP 1B1 Val/Val*					
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p	p	p
Total cholesterol (TC), (mmol/L)	12	5.43	± 0.96	38	5.50	± 0.99	13	5.11	± 0.47	0.415	0.916	0.189
Triglycerides (TG), (mmol/L)	12	1.82	± 0.94	38	1.69	± 1.07	13	1.17	± 0.54	0.112	0.211	0.053
HDL-cholesterol (HDL-C), (mmol/L)	12	1.44	± 0.37	36	1.42	± 0.42	10	1.64	± 0.31	0.292	0.821	0.117
LDL-cholesterol (LDL-C), (mmol/L)	12	3.17	± 0.92	36	3.36	± 0.87	10	2.97	± 0.56	0.402	0.699	0.242
AI1 (TC/HDL-C)	12	3.92	± 0.77	36	4.17	± 1.14	10	3.19	± 0.72	**0.032**	0.911	**0.012**
AI2 (TC-HDL-C)	12	3.99	± 0.73	36	4.12	± 0.99	10	3.42	± 0.62	0.102	0.924	**0.035**
AI3 (LDL-HDL-C)	12	2.25	± 0.60	36	2.55	± 0.89	10	1.90	± 0.61	0.069	0.564	**0.041**
AIP log (TG/HDL-C)	12	0.08	± 0.28	36	0.01	± 0.34	10	-0.24	± 0.26	0.059	0.273	**0.021**

Early postmenopausal status	Hypertensive women									*AM*	*DM*	*RM*
	CYP 1B1 Leu/Leu			*CYP 1B1 Leu/Val*			*CYP 1B1 Val/Val*					
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p	p	p
Total cholesterol (TC), (mmol/L)	26	5.10 ±	1.00	82	5.41 ±	1.07	25	5.80 ±	1.03	0.062	0.089	0.047
Triglycerides (TG), (mmol/L)	26	1.51 ±	0.63	82	1.56 ±	1.41	25	1.80 ±	1.15	0.652	0.801	0.248
HDL-cholesterol (HDL-C), (mmol/L)	23	1.42 ±	0.31	79	1.41 ±	0.43	23	1.44 ±	0.30	0.966	0.985	0.802
LDL-cholesterol (LDL-C), (mmol/L)	23	3.03 ±	0.96	79	3.44 ±	1.10	23	3.77 ±	0.84	0.056	**0.046**	0.082
AI1 (TC/HDL-C)	23	3.75 ±	1.01	79	4.08 ±	1.21	23	4.30 ±	1.29	0.285	0.169	0.282
AI2 (TC-HDL-C)	23	3.69 ±	1.02	79	3.98 ±	1.05	23	4.44 ±	1.11	0.054	0.117	**0.033**
AI3 (LDL-HDL-C)	23	2.24 ±	0.85	79	2.62 ±	1.09	23	2.81 ±	1.08	0.164	0.080	0.264
AIP log (TG/HDL-C)	23	-0.02 ±	0.24	79	-0.01 ±	0.31	23	0.05 ±	0.29	0.629	0.782	0.335

Note: N, number of participants; SD, standard deviation; AI, Atherogenic index; p, value of statistical significance; AM, aditive model (Leu/Leu, Leu/Val, Val/Val); DM, dominant model (Leu/Val + Val/Val vs. Leu/Leu); RM, recesive model (Val/Val vs. Leu/Val + Leu/Leu)

Table 3 shows similar associations to Table 2 between the *CYP1B1* Leu432Val genotypes and the studied variables, but according to the menopausal status of hypertensive women. The Leu432Val genotypes demonstrated statistically significant associations with all atherogenic indices: AI1 (P = 0.032 in the additive model, and P = 0.012 in the recessive model), AI2 (P = 0.035 in the recessive model), AI3 (P = 0.041 in the recessive model) and AIP log (P = 0.021 in the recessive model) in hypertensive pre/perimenopausal women. The mean values of these atherogenic indices were significantly lower in women carrying the Val/Val genotype. (Apart from??) Between other biochemical variables and Leu432Val genotypes there were no observed statistically significant differences in hypertensive pre/perimenopausal women. On the other hand, Leu432Val genotypes in early postmenopausal hypertensive women were statistically significant associated with LDL-C (P = 0.046 in the dominant model) and AI2 (P = 0.033 in the recessive model). The mean values of LDL-C and AI2 were significantly lower in women carrying the Leu/Leu genotype.

Discussion

Genetic polymorphisms of cytochromes P450s may affect the enzyme catalytic activity and have been reported among different populations to be associated with various diseases and adverse drug reactions (Elfaki et al. 2018a). Polymorphisms in *CYP1B1* were reported to be causes of disease phenotypes such as diabetes mellitus (Elfaki et al. 2018b), hypertension or coronary artery disease (CAD) (Mir et al. 2021). Park et al. (2015) reported that *CYP1B1* genetic variations in interaction with the 25-hydroxyvitamin D affect blood pressure, especially in individuals currently being treated for hypertension. Recently, we have revealed that *CYP1B1* rs1056836 was associated with hyperten-

sion in women, while Val allele was a risk factor for the increased hypertension incidence (Falbova et al. 2020).

Since estrogen has an antiatherogenic action along with lipid lowering abilities, and because the products of genes involved in estrogen metabolism markedly regulate estrogen concentrations, associations between the effect of these genes and lipid levels are also expected. Although, there are some studies indicating a significant association between DNA variants in genes related to estrogen biosynthesis and estrogen catabolism with serum lipid and lipoprotein levels, such as *CYP19A1* in Turkish non-obese females (Coban et al. 2015) or *CYP1A1* in Brazilian women of European descent (Almeida et al. 2005), there is a lack of studies tracking the relationship between *CYP1B1* and the lipid profile. In the present study, we have observed a significant association between *CYP1B1* rs1056836 and lipid profile in Slovak hypertensive women. To the best of our knowledge *CYP1B1* polymorphisms have not been investigated in relation to lipid profile in any east central European population study, with the exception of our two previous studies (Luptakova et al. 2012; Cernanova et al. 2018). The first study revealed that *CYP1B1* rs1056836 was responsible for higher values of atherogenic indices in apparently healthy pre-/perimenopausal women without any serious diagnosis; and, the second study observed the significant association between *CYP1B1* rs1800440 and plasma levels of HDL-cholesterol in postmenopausal women. There are, however, several studies that investigated the association of the *CYP1B1* polymorphisms with lipid profile in other countries/regions. In an Indian cohort with CAD the *CYP1B1* rs1056827 was strongly associated with an increased serum levels of cholesterol, HDL-C, and LDL-C (Mir et al. 2021). Hu, Lin and Chen (2008) observed significantly higher mean levels of HDL-C, LDL-C, and TC in workers from a municipal waste incineration plant in Taiwan carrying the *CYP1B1* rs1056836 Val allele than in those carrying the Leu/Leu genotype.

In this study, we found that women in premenopause with Val/Val genotype had significantly lower values of all investigated atherogenic indices than Leu allele premenopausal carriers. Several biological pathways might shed light on this finding. It has been shown that *CYP1B1* catalyzes the metabolism of 17 β-estradiol into reactive metabolites, such as 4-hydroxyestradiol (4-OH-E2) (Smerdova et al. 2014). Since the *CYP1B1* 432Val allele encodes an enzyme with higher activity to 17ß-estradiol than the 432Leu variants (Tang et al. 2000), women possessing the Val allele might have higher levels of 4-OH-E2. Wang and Zhu (2017) found that 4-OH-E2 had a markedly stronger effect in reducing the adipocyte size and serum cholesterol level in female rats compared to 17β-estradiol. Therefore, the *CYP1B1* Val variant, through a higher concentration of 4-OH-E2, may contribute to lower lipid levels in women before the 17 β-estradiol deficit causes the onset of menopause.

There is also a possible explanation for the observed association between *CYP1B1* and lipid profile in postmenopausal women. Accumulating evidence suggests that *CYP1B1* alters the expression of 560 genes in the liver, including PPARγ (Larsen et al. 2015). Duval, Müller and Kersten (2007) reported that PPARα modulates lipoprotein metabolism whereas activation of PPARα results in a reduction of plasma TG levels and in an increase of plasma HDL levels. However, estrogen inhibits the actions of PPARα on lipid metabolism through its

effects on PPARα-dependent regulation of target genes (Yoon 2009). Thus, this association between *CYP1B1* and lipid profile seems to be apparent in postmenopausal women, but not in premenopausal women with functioning ovaries. Moreover, the results of some studies demonstrate that Val/Val genotype is associated with lower *CYP1B1* mRNA expression than the *CYP1B1* Leu/Leu genotype after induction with environmental factors, such as benzo(a)pyrene or smoking (Helmig et al. 2009; Helmig et al. 2010; Helmig et al. 2014). Therefore, *CYP1B1* Val variant may have a lower impact on PPARγ activation than Leu variant, which may probably be reflected in negative changes in serum lipid levels. This evidence can at least partially explain the worse lipid profile in Val/Val genotype carriers in postmenopause detected in our study.

Despite the above studies and our seminal findings, there are also some limitations that need to be acknowledged. As our study was cross-sectional and may have had selection bias during case recruitment, this particular design can limit generalization of our results to all Slovak women. Our study was also limited by the sample size of study women (n = 255). Therefore, we would recommend that future studies enlarge the study sample for a more detailed analysis. Moreover, the role of *CYP1B1* polymorphism in lipid metabolism remains unexplained and the exact mechanism of its likely effect on the lipid profile in pre- and postmenopausal hypertensive women is unclear. Thus, future research into the mechanisms of *CYP1B1* is warranted.

Conclusion

In conclusion, our study results demonstrate that the Leu432Val polymorphism may be associated with the atherogenic indices and LDL-C in hypertensive women. Since the data presented here are the first attempt to associate *CYP1B1* polymorphism with lipid and lipoprotein parameters in hypertensive women, replications of the present findings in larger samples are warranted.

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The Authors' contribution

DF contributed to the conception, design, and performance of the study, and writing of the manuscript. LV participated in collection of data, analysis and interpretation of data, and writing of the manuscript. VCČ participated in collection of data. RB was responsible for the statistical analysis. DS was innovator for the project, participated in the conception, design, data collection andperformance of the study.

Conflict of interest

The authors declare that there is no conflict of interest.

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