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Formerly eclamptic women have lower nonpregnant blood pressure compared to formerly preeclamptic women: a retrospective cohort study

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Abstract

Objective—To compare nonpregnant blood pressure and circulating metabolic factors between formerly preeclamptic women who did and did not deteriorate to eclampsia.

Design—Retrospective observational cohort study.

Setting—Tertiary referral centre.

Population—Formerly preeclamptic women with (n=88) and without superimposed eclampsia (n=698).

Methods—Women who experienced preeclampsia with or without superimposed eclampsia during their pregnancy or puerperium were tested for possible underlying cardiovascular risk factors at least 6 months postpartum. We measured blood pressure and determined cardiovascular and metabolic risk markers in a fasting blood sample. Groups were compared using Mann-Whitney U test, Spearman's Rho test or Fisher's Exact test (odds ratios).

Main outcome measures—Differences in postpartum blood pressures and features of the metabolic syndrome between formerly preeclamptic and formerly eclamptic women.

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Disclosure of interest

All authors declare that there are no conflicts of interest.

Details of ethics approval.

The study protocol was approved by the medical ethical committee of the Radboud University Medical Center (CMO 2007/252) and the medical ethical committee board of Maastricht University Medical Center (MEC 0-4-049). The followed procedures were in conformity to institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulation, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Contribution to the authorship

MPHS performed all analysis of the data and wrote the article. MEAS helped to design the study as well helped with the statistical analysis. MJC and LLHP supported and reviewed the analysis and helped revise the article. SAN participated in the interpretation of the results and discussion.

Results—Formerly preeclamptic women who developed eclampsia differed from their counterparts without eclampsia by a lower blood pressure ($p < 0.01$) with blood pressure correlating inversely with the likelihood of having experienced eclampsia ($p < 0.001$). In addition, formerly eclamptic women had higher circulating C-reactive protein levels than formerly preeclamptic women ($p < 0.05$). All other circulating metabolic factors were comparable. Finally, 40% of all eclamptic cases occurred in the puerperium.

Conclusions—Formerly preeclamptic women with superimposed eclampsia have lower nonpregnant blood pressure compared to their counterparts without neurological sequelae with blood pressure negatively correlated to the occurrence of eclampsia. As about 40% of all eclamptic cases occur postpartum, routine blood pressure monitoring postpartum should be intensified.

Tweetable abstract—Formerly preeclampsics' nonpregnant blood pressure is negatively correlated to the occurrence of eclampsia.

Keywords

preeclampsia; eclampsia; blood pressure

Introduction

Preeclampsia is a complex vascular disease unique to pregnancy defined by hypertension (blood pressure $\geq 140/90$ mmHg) combined with proteinuria (>0.3 g/l) ^{1, 2}. Its pathogenesis involves endothelial dysfunction that is also associated with an increased risk of cardiovascular disease in later life ³. A serious, life-threatening complication in preeclamptic women is eclampsia, defined as the new onset of generalized seizures ^{4, 5}. Although relatively rare (3–6 per 10,000 births), eclampsia carries a major burden on maternal and perinatal morbidity and mortality worldwide ⁶. In the brain, eclampsia relates to edema, haemorrhage and stroke, but also impairment of cognitive function and increased risk for hypertension and cardiovascular disease in later life ^{4, 5, 7}.

Eclampsia is generally accepted to be a form of posterior reversible encephalopathy syndrome (PRES), characterized by vasogenic brain edema notably in the white matter of the parietal and occipital lobes ^{8–12}. Blood-brain barrier (BBB) disruption is the hallmark event in the development of vasogenic brain edema and can occur when blood pressure rises above the upper cerebral autoregulatory limit ¹⁰. However, during pregnancy, a large proportion of eclamptic women had no precedence of hypertension ^{5, 10, 13, 14}. Although animal studies suggest that the cerebral blood flow autoregulatory curve is shifted to higher pressures during pregnancy, it is not known whether biological variations in this curve exist in healthy young women outside of pregnancy ^{15, 16}. It is possible that eclamptic women without significant hypertension had even lower nonpregnant blood pressure resulting in a lower limit of the cerebral autoregulatory curve.

In addition to the rise in blood pressure, circulating factors capable of initiating BBB disruption may be involved increasing the susceptibility to eclampsia in preeclamptic women. Previous studies have shown that increased plasma levels of oxidized low density

lipoprotein (oxLDL), a known key factor in vascular dysfunction in severe preeclamptic women, also increase BBB permeability^{17, 18,19}. Therefore, women with preeclampsia developing eclampsia may differ from their non-eclamptic counterparts by a preexistent abnormal metabolic profile, such as dyslipidemia.

In this study, we hypothesized that formerly eclamptic women differed from women that suffered from preeclampsia only by a lower blood pressure outside of pregnancy. In addition, we explored whether the peripheral levels of metabolic factors related to the metabolic syndrome are more prevalent in the nonpregnant state in formerly eclamptic women than in formerly preeclamptic women.

Methods

Study population

In the period between 1996 and 2010, we screened women with a previous hypertensive pregnancy disorder (such as preeclampsia or eclampsia) several months postpartum for possible underlying cardiovascular risk factors at two tertiary care centers. The study was approved by the Hospital Medical Ethical Committees (Maastricht University Medical Center and Radboud University Medical Center; MEC 0-4-049, 2007/252). In this retrospective observational cohort study, we analyzed the data of all primiparous women enrolled in the screening program with a history of preeclampsia complicated by eclampsia (n=92) versus preeclampsia without eclampsia (n=867). Preeclampsia was defined according to the criteria of the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy². All patients discontinued breastfeeding or hormonal contraceptive use at least 4 weeks before screening. Also, women diagnosed with pre-existing hypertension (hypertension diagnosed before 20 weeks of pregnancy or at the time of screening) were excluded (eclampsia group: n=4; preeclampsia group: n= 169). Hypertension was diagnosed as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, or when women were taking antihypertensive drugs. Further, none of the included women used low-dose aspirin or statins at the time of screening. On the evening before the day of screening all patients refrained from eating, drinking and smoking until screening completion.

Blood pressure measurements

Measurements took place at 8:00 AM in a quiet and temperature-controlled room. All women were positioned in a sitting position with the upper part of the measurement arm at heart level, while the whole arm was relaxed. After an acclimatization period of 30 minutes, arterial blood pressure was recorded at 3-minute intervals for a period of 30 minutes using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL) with a cuff size of 13.5×30.7 cm if upper arm circumference ranged from 27.5 to 36.5 cm or a cuff size of 17×38.6 cm if upper arm circumference ranged from 35.5 to 46 cm. After accumulating 9 measurements, the median systolic, diastolic, mean arterial pressures and median heart rate was calculated and registered.

Measurements of metabolic factors

All blood samples were collected in the morning after an overnight fast. Blood samples were taken for plasma lipid profile, glucose, insulin and renal function. Triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL), uric acid, C-reactive protein (CRP) and glucose were determined using standard automated laboratory techniques. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation²⁰. Plasma insulin concentrations were measured using AutoDelfia time-resolved fluoroimmunoassay. Finally, all women had collected a 24 hour urine sample to determine the presence of proteinuria normalized for creatinine output using normal lab standards.

Statistical analysis

All statistical tests were performed in SPSS version 22. All data are presented as mean $\pm$ standard deviation after being screened for normality using histograms and quantile-quantile plots. Normality of each variable was tested using the Kolmogorov-Smirnov method. All data were analyzed with Mann-Whitney U test. Sub-analysis of the blood pressure data was performed using a linear trend analysis. Further, odds ratios and adjusted odds ratios were calculated using 2×2 contingency tables. Inter-group differences were considered statistically significant when the probability (P) was below 0.05.

Results

Table 1 lists the demographics and clinical characteristics of the women with pregnancy being complicated by preeclampsia, without (PE; n=698) and with superimposed eclampsia (E; n=88). Both subgroups were comparable with respect to age, height, weight, BMI, percentage smokers, and also with respect to time elapsed between delivery and screening. In contrast, both subgroups differed from one another with respect to clinical characteristics of the index pregnancy. Compared to the E-subgroup, we noticed that women in the PE-subgroup had delivered at an earlier gestational age. In addition, the birth weight and birth weight centile were lower in the PE-subgroup compared to the E-subgroup, which was not only due to more severe prematurity but also because of a higher incidence of fetal growth restriction.

At the time of screening, we compared both subgroups with respect to blood pressures and heart rates (Table 2). Importantly, the systolic, diastolic and mean arterial pressure were lower outside of pregnancy in the E-subgroup compared to the PE-subgroup. Also, heart rate was lower in the E-subgroup compared to the PE-subgroup. In addition, our results demonstrate that the blood pressure is negatively correlated with the likelihood of the development of eclampsia (Figure 1). When organizing both subgroups according to different blood pressure quintiles, trend analysis showed a significant negative correlation between blood pressure and the occurrence of eclampsia ($p < 0.001$). Also, odds ratio of the quintile subgroups compared to the 20% lowest blood pressure population showed that women in the 4th and highest quintile group had a significant lower incidence of eclampsia compared to the women in the lowest quintile group (Figure 1). In addition, after adjusting these odds ratios for the type of preeclampsia (early-onset versus late-onset preeclampsia), we still found that women in the 4th and highest quintile group had a significant lower

incidence of eclampsia compared to the women in the lowest quintile group (adjusted odds ratio for women in the 4th quintile group compared to the lowest quintile group: 0.76 (95%CI: 0.59–0.96); adjusted odds ratio for the highest quintile group compared to lowest quintile group: 0.71 (95%CI: 0.55–0.91)). Thus, the type of preeclampsia does not significantly affect the negative correlation between blood pressure and the occurrence of eclampsia.

We also analyzed if women diagnosed with eclampsia differed from their counterparts with respect to contributing signs of an underlying form of metabolic syndrome. The difference in metabolic variables between the 2 subgroups was inconsistent, except for a marginally but significantly higher C-reactive protein (CRP) level in the E-subgroup (Table 3).

To determine whether the occurrence of developing eclampsia relative to childbirth related to any of variables measured at screening, we subdivided all women that suffered from eclampsia. Both antepartum and postpartum E-subgroups were similar with regard to age, height, weight, BMI and percentage of smokers (Table 4). The antepartum E-subgroup differed from the postpartum E-subgroup by delivery at an earlier gestational age, resulting more often in an infant with a lower birth weight and a lower birth weight centile (Table 4). Finally, we investigated if there were any differences in blood pressure or metabolic syndrome constituents between antepartum or postpartum eclampsia. Table 5A and 5B show that blood pressure, heart rate and metabolic indices were similar in both groups. Women in the antepartum E-subgroup showed a trend towards having higher LDL and total cholesterol compared to the postpartum E-subgroup, but those variables did not reach statistical significance. Triglycerides were significantly higher in the postpartum E-subgroup.

Discussion

Main findings

This study provides convincing evidence for formerly eclamptic women to have lower blood pressure and heart rate in the nonpregnant state compared to women that suffered from preeclampsia only. Importantly, blood pressure is negatively correlated with the occurrence of eclampsia. Additionally, formerly preeclamptic patients with or without superimposed eclampsia were comparable with respect to metabolic features, except for slightly higher peripheral levels of CRP after eclampsia.

Strengths and limitations

The main strength is the number of eclamptic women enrolled in the cohort. As our national guidelines advocate blood pressure control above 170/110 mmHg, the relative change is consequently larger in women with lower pre-pregnancy blood pressure. We therefore send out a strong message about the importance of surveillance of the delta of the blood pressure throughout gestation and the puerperium. Unfortunately, we were unable to access data from these women specifying their pre-pregnancy health status and during pregnancy before the onset of preeclampsia/eclampsia, and our speculation should be taken with some caution. Also, although we do not show any underlying metabolic disorder, pregnancy itself may unmask metabolic syndrome that will re-emerge in later life, beyond the time frame for

which this study was conducted. Another limitation is that we did not measure growth factors such as vascular endothelial growth factor (VEGF), soluble Flt-1 (sFlt-1) and placental growth factor (PLGF), which made it impossible to assess their possible involvement/interaction. Finally, the more aggressive management of preeclamptic women throughout the last decade may cause a bias in the eclamptic group.

Interpretation

Eclampsia remains a life-threatening complication of pregnancy and can be considered as a form of PRES, as shown in most eclamptic patients^{12, 14}. Here, we demonstrated that formerly eclamptic women had lower nonpregnant blood pressure compared to formerly preeclampsics with a negative correlation between blood pressure and the occurrence of eclampsia. We can only speculate about the clinical relevance of this finding. Preeclampsia is partly defined by hypertension occurring after 20 weeks of pregnancy in a previously normotensive woman²¹. This definition does not consider the delta of the blood pressure throughout the course of gestation, but may be more important in the development of neurologic complications than the absolute number and thereby should be assessed individually.

One important contributor in the development of vasogenic brain edema and eclampsia is breakthrough of cerebral blood flow autoregulation^{4, 14, 16}. Above the autoregulatory pressure threshold, forced dilation of the cerebral vessels occurs, resulting in hyperperfusion, potentially leading to significant brain tissue damage, vasogenic edema and life-threatening sequels^{14, 22}. Several studies showed a considerable percentage of eclamptic women without significant hypertension^{12, 23}. This has led to the concept that pregnancy may shift the upper limit of autoregulation. Although pregnancy showed to extend the upper limit of the autoregulatory curve during acute hypertension in rats,¹⁴ pregnant rats showed brain edema formation at significantly lower blood pressures compared to nonpregnant rats²⁴. In addition, pregnancy both prevents and reverses medial hypertrophy of cerebral arteries resulting from chronic exposure to hypertension. This effect possibly eliminates the protection against forced dilatation of the preexistent vascular remodelling^{7, 25}. Here, we speculate that preeclamptic women with a relatively low blood pressure outside of pregnancy have a higher risk for eclampsia by autoregulatory breakthrough at a lower blood pressure than their counterparts with a higher nonpregnant blood pressure. However, this hypothesis assumes that blood pressures measured remote from pregnancy reflect antepartum blood pressures and needs to be addressed in future studies.

Additionally, the incidence of postpartum eclampsia has increased at the cost of antepartum eclampsia, probably as a result of intensified surveillance and more active clinical management during pregnancy²⁶. Here, we found about 40% of all eclamptics to occur postpartum, which is comparable with the 30–50% incidence of postpartum eclampsia reported earlier²⁶. Importantly, previous reports indicated postpartum eclampsia often was not preceded by hypertension^{20, 27, 28}. It follows that women with mild hypertension during pregnancy may have blood pressures above their autoregulatory threshold putting them at risk during the puerperium, where blood pressure monitoring is decreased, yet with no

clinical profile to differentiate them from low-risk women. This changing pattern of eclampsia confronts health professionals with the challenge of recognizing women in the puerperium with neurologic symptoms that need prompt referral.

Impaired cerebral autoregulation may not be the only factor associated with an increased risk for preeclampsia/eclampsia. Circulating factors have shown to increase BBB permeability and seizure activity^{17, 18}. For example, preeclampsia is associated with an superimposed dyslipidemia compared to normal pregnancy^{29, 30, 31}. Recent studies demonstrated that elevated levels of oxLDL increase BBB permeability and may be an important contributor to vasogenic brain edema in severe early-onset preeclampsia^{17, 32}. Our results suggest that antepartum eclampsia occurs more often in early-onset preeclampsia, however, did not indicate that eclamptic women already had an underlying metabolic disorder. Nevertheless, previous studies support that women that suffered from severe early-onset preeclampsia have a higher risk of metabolic syndrome and cardiovascular disease in later life compared to women that experienced a normal pregnancy or even suffered from late-onset preeclampsia^{28, 33, 34}. Interestingly, our results demonstrate that formerly preeclamptic patients have higher risk of IUGR compared to formerly eclamptics. If this difference is related to the presence of more severe systemic endothelial dysfunction in preeclampsia compared to a higher prevalence of metabolic syndrome in eclamptic women is not known and needs to be addressed in further studies, especially the correlation to the risk of cardiovascular disease in later life. Thus, a follow-up of this cohort is needed to measure cardiovascular, metabolic, endothelial and cerebral microvessel function. Further, future research is needed to investigate hyperlipidemia in severe early-onset preeclampsia, combined with elevated growth factors such as VEGF and PLGF that could interact and induce oxidative stress. In fact, previous animal studies found that inhibition of VEGF-receptor tyrosine-kinase activity prevented BBB disruption induced by plasma from preeclamptic women¹⁸. The mechanism underlying VEGF-induced BBB permeability in preeclamptic plasma involved release of nitric oxide that binds oxidative radicals generated by activated oxLDL to cause endothelial dysfunction through the formation of peroxynitrite^{17, 35}. Thus, circulating factors that cause oxidative stress and endothelial dysfunction likely have a role in cerebral edema formation during eclampsia.

Finally, CRP was slightly higher in formerly eclamptics compared to formerly preeclampsia. Previous studies found that CRP may have a predictive value in predicting severe preeclampsia and is involved in cardiovascular events^{36–38}. CRP binds to the same receptor as oxLDL, which subsequently induces endothelial dysfunction by releasing toxic oxidative radicals^{17, 19, 32}. Further research is necessary to examine the involvement and clinical significance of CRP in the pathogenesis of (pre)eclampsia.

Conclusion

In absence of metabolic risk factors, formerly eclamptic women have lower nonpregnant blood pressure compared to formerly preeclampsia with a negative correlation between blood pressure and the occurrence of eclampsia. This observation may support the concept that the rate and/or magnitude of the rise of blood pressure rather than the maximum blood pressure at the onset of eclamptic fits could be more important in triggering eclampsia. As

about 40% of all eclamptic cases occur postpartum, surveillance of preeclamptic women during childbirth should include routine blood pressure monitoring postpartum.

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Figure 1.

Percentages of the occurrence of eclampsia (E) versus preeclampsia (PE) arranged in quintile groups of the mean arterial blood pressure (MAP). Graph showing trend-analysis that demonstrates a significant negative correlation between MAP and the occurrence of eclampsia (E). In addition, graph showing odds ratio of 2nd to 5th quintile group compared to the lowest quintile group of the MAP. Odds ratios show a decreased risk of the occurrence of eclampsia when increasing MAP in the different population quintiles that is reaching statistical difference in the 4th and 5th quintile group ($p < 0.05$). Population Quintiles and corresponding MAP: <p20: MAP < 79 mmHg; p20–40: MAP 79–84 mmHg; p40–60: MAP 84–89 mmHg; p60–80: MAP 89–97 mmHg; >p80: MAP > 97 mmHg.

Table 1

Demographics of formerly preeclamptic and eclamptic women.

Indices	PE (n=698)	E (n=88)	<i>P</i>
Age (yrs)	31.0 ± 4.1	30.3 ± 4.5	0.19
BMI (kg/m ²)	25.2 ± 4.9	24.9 ± 4.8	0.67
Height (cm)	168.3 ± 6.5	167.6 ± 6.6	0.51
Weight (kg)	71.4 ± 14.7	70.3 ± 15.1	0.46
Smoking (%)	12	15	0.25
Time between delivery and screening (months)	11 ± 8	11 ± 9	0.81
Index pregnancy			
SGA (<p10;%)	33	20	0.02
Gestational days birth	232 ± 38	242 ± 31	0.01
Gestational weeks birth	33 ^{1/7} ± 5 ^{2/7}	34 ^{6/7} ± 4 ^{3/7}	0.01
Birth weight (grams)	1737 ± 864	2212.9 ± 1000	<0.01
Birth weight centile	28 ± 14	35 ± 19	0.01

BMI = body mass index; SGA = small for gestational age. PE = preeclampsia; E= eclampsia.

Table 2

Nonpregnant blood pressure of formerly preeclamptic vs. eclamptic women.

Indices	PE (n=698)	E (n=88)	P
BP systolic	119 ± 12	111 ± 9	< 0.01
BP diastolic	72 ± 9	67 ± 8	< 0.01
MAP	88 ± 10	83 ± 8	< 0.01
Heart rate (beats per minute)	71 ± 10	68 ± 10	0.03

BP = Blood Pressure; MAP = Mean Arterial Pressure; PE= preeclampsia; E= eclampsia.

Table 3

Nonpregnant metabolic factors formerly preeclamptic vs. eclamptic women.

Indices	PE (n=698)	E (n=88)	P
Proteinuria (mg/mmol)	7.5 ± 3.3	7.3 ± 6.0	0.19
Uric acid (mmol/l)	4.2 ± 1.1	4.3 ± 1.0	0.56
Total cholesterol (mmol/l)	4.7 ± 0.9	4.8 ± 0.9	0.13
HDL (mmol/l)	1.4 ± 0.8	1.3 ± 0.3	0.87
LDL (mmol/l)	3.0 ± 0.8	2.9 ± 0.9	0.38
Triglycerides (mmol/l)	1.1 ± 0.7	1.2 ± 0.7	0.13
Glucose (mmol/l)	5.0 ± 0.7	5.1 ± 1.0	0.75
Insulin (mmol/l)	11.1 ± 5.7	10.5 ± 5.3	0.17
HbA1c	5.2 ± 0.4	5.4 ± 0.8	0.88
CRP (mmol/l)	3.6 ± 2.1	4.8 ± 3.1	0.02

PE = preeclampsia; E= eclampsia; HDL= high density lipoprotein; LDL= low density lipoprotein.; CRP= C-reactive protein.

Table 4

Demographics of formerly antepartum vs. postpartum eclampsia.

Indices	Antepartum (n=53)	Postpartum (n=35)	P
Age (yrs)	30.2 ± 4.1	30.5 ± 4.9	0.73
BMI (kg/m ²)	24.8 ± 4.5	25.0 ± 5.2	0.95
Height (cm)	168 ± 7	168 ± 7	0.94
Weight (kg)	70.0 ± 13.7	70.6 ± 13.4	0.81
Smoking (%)	19	14	0.26
Time between delivery and screening (months)	11 ± 8	12 ± 9	0.50
Index pregnancy			
SGA (<p10)	20	17	0.88
Gestational days birth	222 ± 22	273 ± 9	< 0.01
Gestational weeks birth	31 ^{5/7} ± 5 ^{2/7}	39 ^{0/7} ± 4 ^{3/7}	< 0.01
Birth weight (grams)	1588 ± 847	3123 ± 416	< 0.01
Birth weight centile	30 ± 28	47 ± 25	0.02

BMI = body mass index; SGA = small for gestational age.

Table 5A

Nonpregnant blood pressures in formerly antepartum vs. postpartum eclampsia.

Indices	Antepartum (n=53)	Postpartum (n=35)	<i>P</i>
BP systolic	113 ± 9	111 ± 9	0.29
BP diastolic	68 ± 8	66 ± 6	0.25
MAP	84 ± 8	81 ± 8	0.63
Pulse rate	68 ± 9	68 ± 11	0.87

BP = Blood Pressure; MAP = Mean Arterial Blood Pressure.

Table 5B

Nonpregnant metabolic factors in formerly antepartum vs. postpartum eclampsia.

Indices	Antepartum (n=53)	Postpartum (n=35)	<i>P</i>
Proteinuria (mg/mmol)	7.3 (± 0.7)	7.4 (± 0.4)	0.19
Uric acid (mmol/l)	0.24 (± 0.06)	0.20 (± 0.07)	0.18
Total cholesterol (mmol/l)	4.7 (± 0.9)	4.4 (± 1.0)	0.08
HDL (mmol/l)	1.3 (± 0.4)	1.3 (± 0.6)	0.56
LDL (mmol/l)	2.9 (± 0.6)	2.6 (± 0.8)	0.09
Triglycerides (mmol/l)	1.09 (± 0.7)	1.13 (± 0.7)	0.02
Glucose (mmol/l)	5.2 (± 0.9)	4.9 (± 0.5)	0.89
Insulin (mmol/l)	11.0 (± 5.7)	9.8 (± 4.8)	0.29
HbA1c	5.3 (± 0.9)	5.3 (± 0.4)	0.23
CRP (mmol/l)	4.5 (± 2.9)	4.9 (± 3.0)	0.73

HDL= high density lipoprotein; LDL= low density lipoprotein.