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Low Serum Levels of ABCA1, an ATP-Binding Cassette Transporter, Are Predictive of Preeclampsia

Lixing Liu,[1] Min Zhang,[2] Xianhui Min[3] and Lixi Cai[4]

[1]Department of Anatomy, Basic medical department of Putian College, Putian, Fujian, P.R. China
[2]Department of Physiological, Basic medical department of Putian College, Putian, Fujian, P.R. China
[3]Department of Obstetrics and Gynecology, First Hospital Affiliated to Fuzhou General Hospital, Putian, Fujian, P.R. China
[4]Department of Biochemical, Basic medical department of Putian College, Putian, Fujian, P.R. China

Preeclampsia is a pregnancy-specific disorder characterized by hypertension and proteinuria, but the exact cause of preeclamptic hypertension remains unknown. ATP-binding cassette subfamily A member 1 (ABCA1) reverses cholesterol transport and eliminates excess cholesterol from tissues, whereas higher levels of cholesterol may lead to hypertension. Thus, ABCA1 affects the blood lipid profile. We have hypothesized that serum ABCA1 levels may influence the onset of hypertension and increase the risk of preeclampsia. To test this hypothesis, we measured serum ABCA1 levels in 50 normal pregnancies, 36 preeclamptic pregnancies, and 24 small-for-gestational-age (SGA) pregnancies during three trimesters. We also measured the concentrations of serum ABCA1 in non-pregnant women (n = 60), showing its normal ranges of 0.16 to 0.52 ng/ml. Importantly, the serum levels of ABCA1 were similar among non-pregnant women, normal pregnancies and SGA pregnancies. In contrast, the serum ABCA1 levels were significantly lower in preeclamptic pregnancies (0.06 ± 0.03 ng/ml) than those in non-pregnant women, and normal and SGA pregnancies (P < 0.05). Low serum ABCA1 levels were associated with the increases in the concentrations of blood lipid (low density lipoprotein cholesterol, total cholesterol and triglycerides) and with the decrease in the concentration of high-density lipoprotein cholesterol (P < 0.01), all of which may contribute to the onset of hypertension and eventually preeclampsia. Moreover, the preeclamptic pregnancy was diagnosed with high sensitivity from the nulliparous pregnancies if the cutoff value for serum ABCA1 was 0.06 ng/ml. Thus, low serum levels of ABCA1 are predictive of preeclampsia.

Keywords: ABCA1; blood lipid; hypertension; preeclampsia; SGA pregnancy
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Introduction

Preeclampsia is a hypertensive syndrome that occurs in pregnant women with persistent hypertension (blood pressure of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic), proteinuria (urinary excretion of ≥ 0.3 g protein/24 h) and systemic involvement after 20-week gestation (Woelkers et al. 2015). In addition to preeclampsia, there are four categories of hypertension in pregnancies: 1) Preeclampsia-eclampsia (elevated blood pressure after 20-week gestation with proteinuria or any severe feature of preeclampsia); 2) Chronic hypertension predates pregnancy; 3) Chronic hypertension with superimposed preeclampsia (chronic hypertension associated with preeclampsia); and 4) Gestational hypertension (elevated blood pressure after 20-week gestation in the absence of proteinuria or any severe feature of preeclampsia) (Leeman and Fontaine 2008). Preeclampsia is one of the leading causes for maternal disorders and neonatal mortality and affects 3% to 8% of all pregnancies in the world (Plaks et al. 2013). Preeclampsia more often affects nulliparous pregnant women (Kenny et al. 2014). Despite the extensive studies on preeclampsia, the etiology of the disease is still unknown. Early termination of pregnancy is one of the main treatments for the patients with severe preeclampsia (Haddad et al. 2010). The efficient diagnosis and prediction method for preeclampsia is still unavailable (Hagmann et al. 2012). The high efficient and safe way for precise diagnosis of preeclampsia is needed.

It is important to explore the cause of hypertension since preeclampsia is a hypertensive syndrome. Hypertensive patients are commonly associated with dyslipidemia, which significantly affects blood pressure and lipid profile (Choudhury et al. 2014). ATP-binding cassette subfamily A

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Correspondence: Lixing Liu, Department of Anatomy, Basic medical department of Putian College, Xueyuan Middle Street 1133, Putian, Fujian 351100, P.R.China.
e-mail: lixingfj@163.com

member 1 (ABCA1) is one of the membrane-associated proteins (Shao 2012) and is involved in cholesterol efflux to the serum (Duong et al. 2006). Thus, ABCA1 affects the blood lipid profile (Genvigir et al. 2008). The functions of ABCA1 in the reverse cholesterol transport system for high-density lipoprotein cholesterol (HDL-C) have been reported (Ye et al. 2011). ABCA1 also plays an important role for lipid metabolism of macrophages and its expression was upregulated in macrophages (Schmitz et al. 1999). Indeed, macrophages represent one of main sources of serum ABCA1. Furthermore, macrophage numbers are abnormally high in preeclampsia (Reister et al. 1999). These macrophages highly expressed ABCA1, which may increase the serum ABCA1 in preeclamptic pregnancies. Because ABCA1 plays an important role in lipid metabolism, the functional changes of ABCA1 were associated with variation in serum lipids (Genvigir et al. 2008). ABCA1 controls the reverse cholesterol transport and its variants are associated with changes of serum HDL-C and other lipids (Coban et al. 2014). Moreover, the polymorphism of the ABCA1 gene was found to increased blood pressure, resulting in hypertension in a Japanese population (Yamada et al. 2008).

Serum ABCA1 concentrations show a good relation with ABCA1 levels in tissues ($r = 0.384$, $P < 0.01$) (Liu et al. 2014), and the serum levels of ABCA1 may reflect the total levels of ABCA1 in individuals. Thus, low levels of ABCA1 reflect the lipid abnormality, which may promote the development of hypertension and increase the risk of preeclampsia (Yamada et al. 2008; Ghossein-Doha et al. 2014).

We have hypothesized that ABCA1 may be a potential biomarker for predicting the risk of preeclampsia. In this context, the low levels of ABCA1 in the placenta have been reported to be associated with gestational disease (Baumann et al. 2013). The decreased levels of ABCA1 in placental tissues are closely related with the development of preeclampsia (Albrecht et al. 2007; Baumann et al. 2013). However, predicting the development of preeclampsia is still difficult. It is also unknown whether measuring serum ABCA1 is a simple way for the early prognosis for the risk of preeclampsia. Here, we explored the predictive value of serum ABCA1 in pregnancies with preeclampsia.

Materials and Methods

Participants

All experimental procedures were approved by the Ethnic Committee of First Hospital Affiliated to Fuzhou General Hospital (Putian, Fujian Province, China).The study was performed in the Department of Obstetrics and Gynecology, First Hospital Affiliated to Fuzhou General Hospital. From March 2010 to June 2013, a total of 200 pregnancies were recruited after obtaining written consents from them. All the pregnancies were from Putian city (Fujian Province, China) with normal liver and kidney functions. Other parameters, such as pulmonary function, chest radiography and electrocardiography (ECG), were all in normal ranges. The risks of recurrent preeclampsia are affected by age, body mass index (BMI) and life habits. Thus, all these parameters were constrained to keep fewer heterogeneous results between patients and healthy controls. Finally, 110 pregnancies were recruited including 36 pregnancies (no multiple-gestation) with developed preeclampsia, fifty women with normal pregnancies (no multiple-gestation) and no any major disorders such as diabetes, hypertension, and preeclampsia, and 24 women (no multiple-gestation) who delivered a small-for-gestational-age (SGA) infant. Just like normal pregnancies, SGA pregnancies had no major complications, such as hypertension, preeclampsia, and diabetes, with normal amniotic fluid volume (AFV) (Sandlin et al. 2014) and umbilical artery Doppler (UAD) (Sarno et al. 2014). For comparison, 60 non-pregnant women (32.4 ± 2.5 years) were also recruited in the present study.

Inclusion criteria

The inclusion criteria were used according to a previous report (Ghosh et al. 2012). Briefly, the patients were considered with preeclampsia if the blood pressure ≥ 140/90 mmHg. The patients presented with the symptoms of persistent headache, blur vision, epigastric pain, insufficient urine output (≤ 400 ml/d), platelet count ≤ 100,000/mm^3, and increased alanine aminotransaminase (ALT), aspartate transaminase (AST), and/or lactate dehydrogenase (LDH), compared with those in normal and SGA pregnancies.

Exclusion criteria

The patients would be excluded if they had diabetes, renal failure, cardiovascular disorders, bleeding disorders, autoimmune disorders, epilepsy, tuberculosis or congenital defects. The patients were also excluded if they have taken medicine for more than three months.

Blood lipid assay

The data of blood samples and Doppler ultrasonography were collected during a screening program for nuchal translucency in the first trimester (from 11th to 14th week), the anomaly check in the second trimester (from 20th to 26th week) and the growth pattern in the third trimester (from 28th to 35th week). For all subjects, the concentrations of low-density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol (TC) and triglycerides (TG) were measured in the serum using enzymatic-colorimetric methods by a Beckman spectrophotometer (Beckman, USA). All reagents were purchased from Roche Diagnostics GmbH (Mannheim, Germany).

ELISA for ABCA1

The serum concentrations of ABCA1 were measured using an ABCA1 ELISA kit according to manufacturer's instructions (Shanghai solarbio Bioscience & Technology Co., LTD, Shanghai, China).

Statistics analyses

All the data were analyzed by a SPSS (statistical Package for social science) package 21.0 version. AS standard unimodal distribution curve was plotted to determine the cutoff values of ABCA1 for screening preeclamptic patients with high sensitivity. The association for the concentrations between serum ABCA1 and each plasma lipid was investigated using the post hoc test of Fisher's protected least significant difference.

Results

The characteristics of participants

There was no significant difference in the age between normal and preeclamptic pregnancies. However, the age of pregnancy that delivered an SGA infant was lower ($P < 0.05$) than that of preeclamptic pregnancies (Table 1). Maternal BMI was higher in preeclamptic pregnancies ($P < 0.05$) compared with normal and SGA pregnancies in the first trimester. There was no statistically significant difference among the three groups in relation to smoking, but parity was higher in preeclamptic pregnancies. The pulsatility index was significantly higher in preeclampsia pregnancies compared with normal pregnancies in the second and third trimesters ($P < 0.05$), but not in the first trimester ($P > 0.05$). There was no significant difference in the pulsatility index between normal pregnancies and SGA pregnancies, irrespective of the trimester ($P > 0.05$). Preeclampsia pregnancies showed significantly higher systolic and diastolic blood pressure in the third trimester compared with the normal and SGA pregnancies ($P < 0.01$). There was no significant difference in the mean gestational ages at delivery between normal pregnancies and SGA pregnancies, but the time was half a month earlier in preeclamptic pregnancies ($P < 0.05$). Average weight of neonates born from preeclamptic pregnancies as well as from SGA pregnancies were lower ($P < 0.05$) than the weight of neonates from normal pregnancies. Median weight percentile of SGA neonates was lower ($P < 0.05$) than that from normal pregnancies. The median birth

Table 1. Demographic characteristics at baseline.

	Normal pregnancies	Preeclamptic pregnancies	SGA pregnancies
Cases	50	36	24
Gestational age at first trimester (years)	33.2 ± 3.9◆	35.4 ± 4.3◆	29.6 ± 4.8*
Parity (% nulliparus)	48%	69%	51%
Smokers (%)	18%	21%	20%
Maternal BMI at first trimester (kg/m^2)	25.2 ± 4.1*	29.0 ± 5.2△◆	25.6 ± 4.3*
Doppler PI of uterine artery			
First trimester	1.68 ± 0.36	1.71 ± 0.39	1.76 ± 0.48
Second trimester	1.02 ± 0.34*	1.31 ± 0.44△◆	1.04 ± 0.28*
Third trimester	0.79 ± 0.16*	1.02 ± 0.36△◆	0.81 ± 0.17*
Mean blood pressure at third trimester			
Systolic (mmHg)	108 ± 10*	146 ± 6△◆	106 ± 8*
Diastolic (mmHg)	77 ± 8*	89 ± 10△◆	69 ± 6*
Gestational age at delivery (weeks)	38.9 ± 0.9*	36.1 ± 2.8△◆	39.0 ± 0.7*
Birth weight (g)	3,216 ± 532*◆	2,278 ± 825△◆	2,711 ± 231*△
Birth weight percentile (median, range)	44 (12-94)*◆	22 (3-89)△◆	8 (2-12) *△
Blood lipids — First trimester			
TC, mM	4.35 ± 0.28	4.57 ± 0.29◆	4.17 ± 0.22*
TG, mM	3.25 ± 0.27	3.38 ± 0.25◆	3.01 ± 0.24*
LDL-C, mM	3.24 ± 0.08	3.46 ± 0.11◆	2.98 ± 0.12*
HDL-C, mM	2.06 ± 0.52*	1.45 ± 0.26△◆	1.89 ± 0.45*
Second trimester			
TC, mM	4.71 ± 0.32*◆	5.29 ± 0.26△◆	4.36 ± 0.29*△
TG, mM	3.64 ± 0.29*◆	4.27 ± 0.33△◆	3.28 ± 0.31*△
LDL-C, mM	3.55 ± 0.10◆	3.86 ± 0.15◆	3.14 ± 0.09*△
HDL-C, mM	1.98 ± 0.17*	1.35 ± 0.19△◆	1.86 ± 0.24*
Third trimester			
TC, mM	5.21 ± 0.30*◆	6.34 ± 0.25△◆	4.71 ± 0.32*△
TG, mM	3.68 ± 0.32*	4.69 ± 0.27△◆	3.44 ± 0.23*
LDL-C, mM	3.80 ± 0.16*◆	4.29 ± 0.19△◆	3.31 ± 0.11*△
HDL-C, mM	1.83 ± 0.36*	1.31 ± 0.25△◆	1.81 ± 0.37*

SGA, small for gestational age, infants whose weight was less than the 10th percentile for gestational age; BMI, body mass index, body mass divided by the square of height; PI, pulsatility index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. *$P < 0.05$ compared with preeclamptic pregnancies. △$P < 0.05$ compared with normal pregnancies. ◆$P < 0.05$ compared with SGA pregnancies.

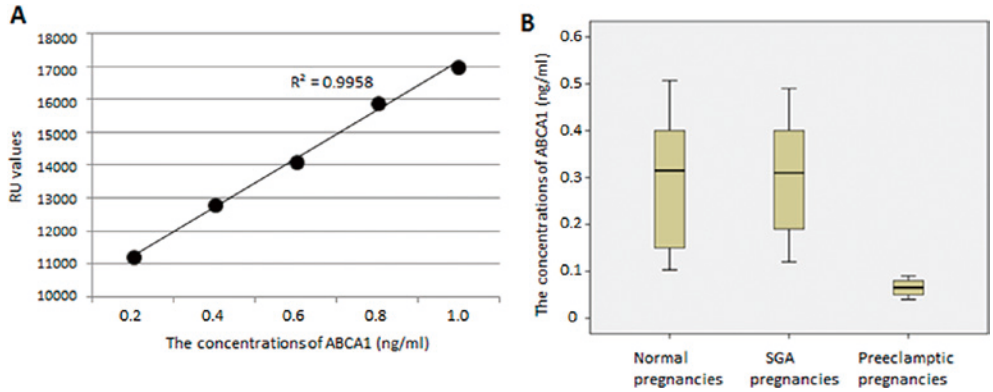

Fig. 1. Comparison of serum ABCA1 levels among normal, preeclamptic, and SGA pregnancies.
(A) Serum ABCA1 was measured by ELISA. A standard curve was plotted between the concentrations of ABCA1 and absorbing value at 450 nm. (B) Bar diagram indicated the difference in serum ABCA1 levels among different pregnancies in the first trimester. The data shown (n = 110) include 50 normal pregnancies, 36 preeclamptic pregnancies, and 24 SGA pregnancies.

weight percentile of neonates born from preeclamptic women was also lower ($P < 0.05$) than that of normal pregnancies.

There were statistically significant differences in the concentrations of serum TC, TG, LDL-C, or HDL-C among preeclamptic, normal and SGA pregnancies ($P < 0.05$) (Table 1). The concentrations of lipids (TC, TG, and LDL-C) were lowest in SGA pregnancies compared with those in preeclamptic and normal pregnancies. Moreover, the concentrations of lipids were highest in preeclamptic pregnancies ($P < 0.05$). In contrast, the concentration of HDL-C was lowest in preeclamptic pregnancies compared with SGA and normal pregnancies ($P < 0.05$), while the HDL-C concentration was highest in normal pregnancies. The results showed an increase in the levels of TC, TG and LDL-C and a decrease of HDL-C from the first trimester to the second trimester and from the second trimester to the third trimester in three groups.

Serum levels of ABCA1 protein

The concentrations of ABCA1 in serum were determined using a standard curve (Fig. 1A). The concentrations of ABCA1 were 0.3 ± 0.2 ng/ml (95% CI: 0.15-0.42 ng/ml) for normal pregnancies, 0.32 ± 0.19 ng/ml (95% CI: 0.12-0.49 ng/ml) for SGA pregnancies, and 0.06 ± 0.03 ng/ml (95% CI: 0.08-0.04 ng/ml) for preeclamptic pregnancies in the first trimester (Fig. 1B). Apparently, the low serum levels of ABCA1 were associated with preeclampsia ($P < 0.01$). However, there was no significant difference in serum ABCA1 levels between normal and SGA pregnancies.

We also measured the serum ABCA1 levels in non-pregnant women (n = 60, 32.4 ± 2.5 years), showing the normal ranges of serum ABCA1 (0.16 to 0.52 ng/ml). There was no significant difference in normal ranges of serum ABCA1 between non-pregnant women and normal pregnant women.

The serum levels of ABCA1 were significantly different between normal and preeclamptic pregnancies (Table 2). There were no significant changes in the serum levels of ABCA1 between the first trimester and the second trimester and between the second trimester and the third trimester in normal and SGA pregnancies ($P > 0.05$). There was a significant change between the first trimester and the third trimester in normal and SGA pregnancies ($P < 0.05$). In contrast, the serum levels of ABCA1 decreased significantly from the first trimester to the second trimester, from the first trimester to the third trimester, and from the second trimester to the third trimester in preeclamptic pregnancies ($P < 0.05$).

Serum ABCA1 affects the concentration of plasma lipids

The Spearman's rank correlation coefficient showed the stringent relationship between serum ABCA1 levels and the concentration of plasma lipids. Low serum levels of ABCA1 levels were associated with the increases in the concentrations of atherosclerosis risk factors TC ($P < 0.01$) (Fig. 2A), TG ($P < 0.01$) (Fig. 2B) and LDL-C ($P < 0.01$) (Fig. 2C), and with the decrease in the concentration of atherosclerosis-protector HDL-C ($P < 0.01$) (Fig. 2D) in all the subjects, all of which may contribute to the onset of hypertension and eventually preeclampsia. In the same trend, low serum levels of ABCA1 were associated with the increases in the concentrations of atherosclerosis risk factors TC ($P < 0.01$), TG ($P < 0.01$) and LDL-C ($P < 0.01$), and with the decrease in the concentration of atherosclerosis-protector HDL-C ($P < 0.01$) in normal pregnancies, SGA pregnancies and preeclamptic pregnancies. These results also suggest that ABCA1 may significantly affect blood lipid profiles.

Cutoff values for serum ABCA1

The serum levels of ABCA1 were lowest in preeclamptic pregnancies compared with those in normal and SGA pregnancies in three trimesters (Table 2, $P < 0.05$). Thus, the cutoff values for serum ABCA1 were evaluated in

Table 2. Serum ABCA1 levels (ng/ml) in normotensive and preeclamptic women with different gestational age.

Gestational age	Normal pregnancies	Preeclamptic pregnancies	SGA pregnancies	*P* value
First trimester	0.305 ± 0.202	0.063 ± 0.027	0.315 ±0.193	P1,2 = 0.000
				P1,3 = 0.778
				P2,3 = 0.000
Second trimester	0.281 ± 0.1445	0.050 ± 0.023	0.299 ± 0.122	P1,2 = 0.000
				P1,3 = 0.613
				P2,3 = 0.000
Third trimester	0.270 ± 0.171	0.043 ± 0.016	0.289 ± 0.242	P1,2 = 0.000
				P1,3 = 0.521
				P2,3 = 0.000
P value	P1 = 0.419	P1 = 0.013	P1 = 0.431	
	P2 = 0.041	P2 = 0.004	P2 = 0.048	
	P3 = 0.212	P3 = 0.026	P3 = 0.448	

P1, P2, P3 stand for the *P* value for the statistics significance for the serum ABCA1 levels between the first trimester and the second trimester, between the first trimester and the third trimester, and between the second trimester and the third trimester weeks. P1,2, P1,3 and P2,3 stand for the *P* value for the statistics significance for the serum ABCA1 levels between normal pregnancies and preeclamptic pregnancies, between normal pregnancies and SGA pregnancies, and between preeclamptic pregnancies and SGA pregnancies. All the statistics significance was calculated via *t*-test.

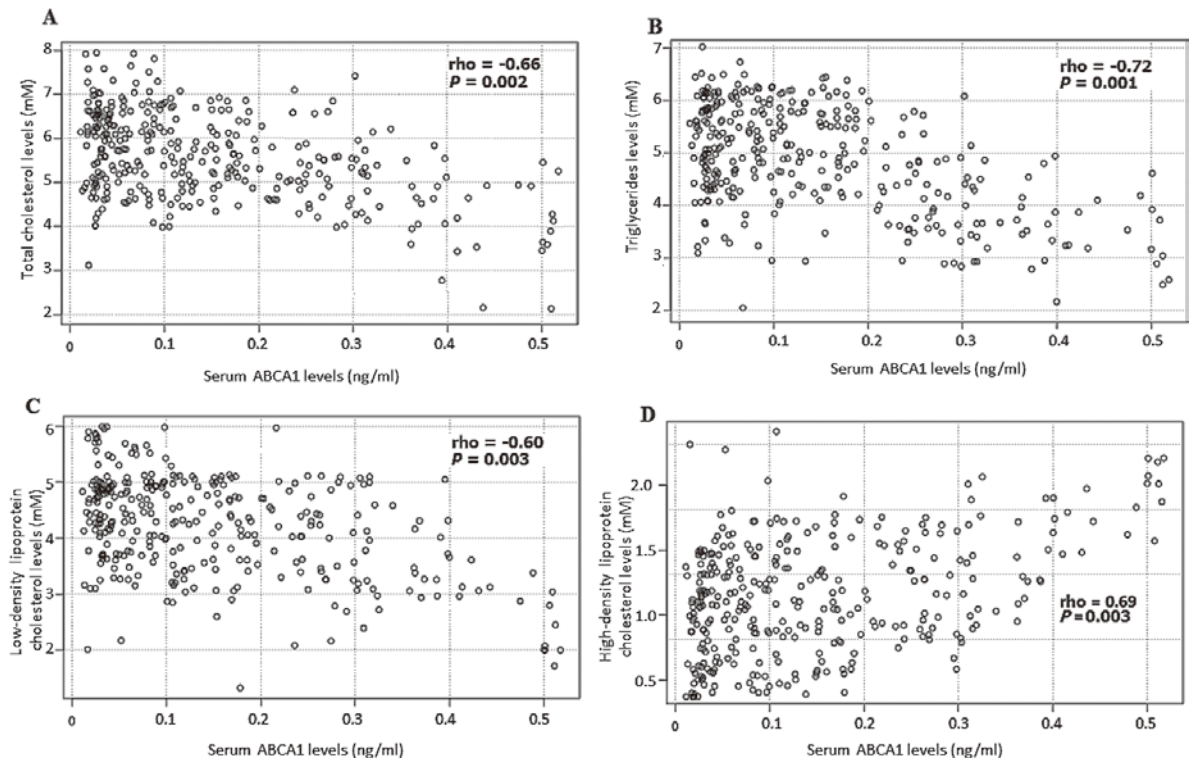

Fig. 2. The relationship between serum ABCA1 levels and plasma lipid levels.
(A) The relationship between serum ABCA1 levels and TC levels. (B) The relationship between serum ABCA1 levels and TG levels. (C) The relationship between serum ABCA1 levels and LDL-C levels. (D) The relationship between serum ABCA1 levels and HDL-C levels. The data shown (n = 110) include 50 normal pregnancies, 36 preeclamptic pregnancies, and 24 SGA pregnancies. Statistical analysis was preformed with Spearman's rank correlation test. The value of rho between −1 and −0.5 indicates a reverse correlation; the value between 0.5 and 1 indicates a good correlation. In each relationship, there is statistically significant difference ($P < 0.01$).

the preeclampsia women. According to the values of serum ABCA1, it was possible to predict preeclampsia. The cutoff value of serum ABCA1 was determined via a standard unimodal distribution curve. To keep high sensitivity, the cutoff point included 95% of serum ABCA1 values among all preeclamptic pregnancies. The values

were significantly lower in preeclampsia women than those in normal and SGA pregnancies. Thus, we suggested that the cutoff value was less than 0.06 ng/ml for serum ABCA1 at gestation, and then preeclamptic pregnancies could be diagnosed in the nulliparous pregnant women.

Discussion

Here we aimed to correlate serum ABCA1 levels with the severity of preeclampsia and to explore the prognosis values of the biomarker in preeclamptic pregnancies. This is the first case-control study conducted in a Chinese Han population to explore the values of serum ABCA1 in pre-eclampsia detection. Our findings suggested that low serum ABCA1 levels were associated with the risk of preeclampsia.

Many biomarkers for the diagnosis of preeclampsia have been reported (Textoris et al. 2013; Maynard et al. 2013; Palominos et al. 2014). However, these biomarkers are still far from for clinical usage. Thus, the high efficient and safe biomarkers are still needed. Here, we showed the lower serum ABCA1 levels in preeclamptic pregnancies; namely, measuring serum ABCA1 provides a simple, effective, and safe method for the early diagnosis of the preeclampsia. The serum ABCA1 offered a high-sensitive way for preeclampsia detection among all pregnancies at gestation, and this method can be utilized for preeclampsia prediction in nulliparous pregnant women. Although preeclampsia occurs at any time during the pregnancy period, a significantly large number of nulliparous pregnant women have high-risk preeclampsia in the late second trimester. Therefore, we hope that the method can be used for preeclampsia detection.

Here, the molecular mechanisms were explored for the role of ABCA1 in the progression of preeclampsia. Low serum ABCA1 levels were associated with the increase of LDL-C levels, suggesting that the lower serum ABCA1 may increase the risk of atherosclerosis. LDL-C may accelerate the deposition of cholesterol in the arteries of preeclampsia women, while decreased atherosclerosis-protector HDL-C may inhibit the process that the cholesterol is transported to liver via the circulation of blood. These changes may exacerbate the injury of endothelial cell because of the release of endothelial cell factors such as lipid peroxide into the blood circulation of pregnancy women. Thus, the permeability of vascular endothelial cells increases and stimulates that the monocytes enter into vessels and form macrophage-derived foam cells. Subsequently, athermanous plaque will be formed because of the accumulation of cholesterol. All these results finally induce a cascade of pathological and clinical changes of hypertension (Winquist and Steenland 2014), which results in preeclampsia (Sarno et al. 2015).

The setup of the cutoff value for preeclampsia increased the sensitivity of diagnosis since the preeclampsia disease is prevalent in a pregnancy population. The high specificity and early detection is highly desired since the disease is lethal. However, the high specificity will increase the cost of the sensitivity of the diagnosis for preeclampsia. Thus, the cutoff value was chosen at a median level. In the worldwide, traditional methods for considering the risk factors, such as maternal age, family history, preexisting diseases, etc., for evaluating the developing preeclampsia, have been the big problems because most pregnancies have specific risks but they do not develop preeclampsia. In the most cases, diagnosis of preeclampsia is only made when the symptoms are magnified. Therefore, it is necessary to explore the potential biomarkers for predicting the onset of preeclampsia. Here, measuring serum ABCA1 offers a simple, safe and effective method for the early diagnosis of onset and development of preeclampsia.

ABCA1 has been reported to exist in many tissues such as liver, testis, adrenal and placental tissue (Wellington et al. 2002; Liu et al. 2014). If so, we can assume that the serum levels of ABCA1 may be higher in normal pregnant women than those in non-pregnant women. However, there was no significant difference in normal ranges of serum ABCA1 (0.16 to 0.52 ng/ml) between non-pregnant women and normal pregnant women. These results suggest that the serum ABCA1 may be derived from non-placental tissues. Meanwhile, all these results suggest that ABCA1 can be expressed in many tissues and has multiple functions.

There are some limitations in the present work. No cost and cost-effectiveness analyses were assessed. The data were not stratified by severity of preeclampsia. The work was not conducted in a larger population, so it is necessary to be conducted in a larger population to enhance the validity of the results. ABCA1 is a unique protein that functions as an integral membrane protein and is also present in serum. Much work is needed to address these problems. Further work is needed in the future for better understanding the molecular mechanism in more detail for causing preeclampsia.

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Conflict of Interest

The authors declare no conflict of interest.

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