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ORIGINAL ARTICLE

The relationship between hypertension and plasma allantoin, uric acid, xanthine oxidase activity and nitrite, and their predictive capacity in severe preeclampsia

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It is controversial that uric acid (UA) levels are related to the severity of hypertension in preeclampsia (PE). Our aim in this study was to determine whether UA, xanthine oxidase activity (XOA), allantoin and nitrite levels are related to arterial blood pressure (BP) in PE. We formed a control group ($n = 20$) and a PE group ($n = 20$) for the study. Their BPs and plasma UA, XOA, allantoin and nitrite levels were measured. The values from the control and PE pregnant women were assessed via a Wilcoxon matched-pairs test. A Pearson correlation test was also performed. In addition, the diagnostic value of these tests was evaluated via receiver operating characteristic (ROC) analysis. The BP, UA, XOA and allantoin levels in the PE patients were found to be higher when compared with those of the pregnant controls. The UA, XOA and allantoin levels showed high correlations with BP in cases of PE. However, there was no superiority among the correlations. No differences were observed between the groups in terms of nitrite levels and the relationship between nitrite and BP. UA, XOA and allantoin levels may be high due to placental cell death because of abnormal trophoblastic activity observed in PE. Moreover, the reactive oxygen products that are created during the genetic material degradation may explain how UA, XOA and allantoin levels are related to BP. According to ROC analysis, UA, XOA and allantoin assays are reliable predictors for the determination of PE.

Keywords: Allantoin, nitrite, preeclampsia, uric acid, xanthine oxidase activity

Introduction

Preeclampsia (PE) is a common, severe disease that occurs in pregnancy. It is a major cause of maternal and foetal morbidity and mortality. The main features of the disease are de novo hypertension after 20 weeks' gestation and proteinuria; it is also frequently accompanied by oedema and other subjective symptoms (Alasztics et al. 2012). Hyperuricaemia is associated with the severity of PE (Bellomo et al. 2011; Redman et al. 1976; Sagen et al. 1984). PE is also characterised by increased free radical formation and elevated levels of oxidative stress (Many et al. 1996). In previous studies, it was found that xanthine oxidase activity (XOA) is increased in PE (Karabulut et al. 2005; Yildirim et al. 2004). When XO catalyses the oxidation of hypoxanthine to xanthine and further catalyses the oxidation of xanthine to uric acid (UA), reactive oxygen species are generated. Lamarca et al. mentioned that endothelial dysfunction and decreased renal function due to reactive oxygen species is a reason for hypertension in PE (Lamarca 2012).

In previous studies, although UA and XOA have been shown to be increased in PE, the relationship of UA and XOA to arterial blood pressure (BP) has not yet been identified (Cnossen et al. 2006; Koopmans et al. 2009; Mustafa et al. 2012; Thangaratinam et al. 2006). In studies carried out on essential (primary) hypertension patients, it has been reported that there may be an association of BP with UA and XOA (Feig et al. 2008; Loeffler et al. 2012; Newaz et al. 1996). UA and XOA are greatly increased in PE. For this reason, it may be expected that UA and XOA, together with BP, may have a relationship in cases of PE. This hypothesis was tested in the present study.

Allantoin is a non-enzymatic oxidative product of UA in humans. If UA levels increase, allantoin – a product of UA – level will naturally increase. Moreover, it has been shown that the rate of formation of allantoin from UA is higher under oxidative stress conditions (Kand'ar and Zakova 2008; Zitnanova et al. 2004). The allantoin increase may be higher than the increase in UA due to the high level of UA and oxidative stress during PE. If UA has a relationship with BP in PE, the relationship between allantoin and BP may be even greater for the abovementioned reasons.

Nitric oxide (NO) becomes nitrite under oxidative conditions (Lundberg et al. 2008). If oxidative reactions increase in cases of PE and NO-to-nitrite transformation occurs, then the level of nitrite may also increase in PE. This increase may be related to BP in PE.

Based on the above-mentioned hypotheses, we examined the relationship of plasma UA, XOA, allantoin and nitrite levels with BP in pregnant women with PE. If UA, XOA, allantoin or nitrite levels are high and there is a relationship with BP in PE, these parameters may help to predict PE. Thus, the UA, XOA, allantoin and nitrite levels were measured in control and PE groups. The relationships of these parameters with systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were tested, as well as the superiority amongst these relationships. In addition, receiver operating characteristic (ROC) analyses were performed to evaluate the diagnostic values of these parameters.

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Materials and methods

Subjects

We received approval from the Akdeniz University Clinical Ethics Committee for this study. The pregnant women who applied to the Akdeniz University Faculty of Medicine Gynaecology Clinic for routine health examinations were selected as subjects. The PE group ($n = 20$) was formed from pregnant women who were diagnosed as having PE according to the American gynaecology and birth association criteria (ACOG Committee on Obstetric Practice 2002). Pregnant women selected as control group ($n = 20$) were selected at random from all women based on the following criteria: the same gestational age (± 3 years) and maternal age (± 2 weeks) as the pre-eclamptic women. Only nulliparous pregnant women, who were pregnant for the first time, were accepted for the study. Pregnant women accepted as subjects attended our hospital from 9 a.m. to 11 a.m. After the physical examination, blood samples were taken at time of diagnosis of PE. In both groups, pregnant women who took medication for whatever reason were excluded from the study because of the consideration that medication could change their blood parameters. In the control group, pregnant women who had anomalies in terms of clinical and laboratory findings were not included in the study. The pre-eclamptic pregnant women who had clinical and laboratory abnormalities other than the findings of preeclampsia disorder were excluded from the pre-eclamptic group. In addition, patients who had chronic diseases were excluded from this study.

Blood pressures

The blood pressures of the subjects were obtained during the first examination. They were measured after a 15-min rest in a sitting position via a sphygmomanometer (ERKA, Germany). MAPs were measured via the MAP = 1/3(SBP-DBP)+ DBP formula.

Blood samples

The venous blood samples of the subjects were collected from the collective venous blood vessels of the forearm with EDTA-containing sterile tubes. Each blood sample had a volume of 6 ml. The blood samples were centrifuged at + 4°C for 5 min at 2,000 × g, and their plasmas were separated. Then, 2 ml of plasma was placed in centrifuge tubes with membranes designed to retain molecules over 10,000 kDa (Millipore, Amicon Ultra-4, County Cork, Ireland), centrifuged at 1,500 × g for 30 min and filtered. The ultrafiltrate was divided into two identical volumes to be used in measuring xanthine, allantoin, UA and nitrite. After the centrifugation, the intensified plasma on the membrane in the centrifuge tube was placed in a column that contained 10 ml of swollen Sephadex G25 (Farmacia, Sweden), passed through 3 ml (pH: 8.5, 50 mM) of + 4°C phosphate buffer and collected as an eluate-rich protein 4 ml in volume (Marti et al. 2004; Marti et al. 2001). The eluate–xanthine was divided into two volumes of 2 ml each, which were to be used in oxidase measurement.

Determination of allantoin, xanthine and uric acid

All of the chemicals used for measurements were obtained from Sigma Chemical Company (St. Louis, MO, USA). The measurements were performed using a single injection via high-performance liquid chromatography (HPLC). The device used was a Hewlett Packard 1100 system. A YMC ODS-AM (4.6 × 250 mm, 5 µm, AM-303, Schermback, Germany) inverted-phase HPLC column was employed. Using a 40-µl sample at room temperature at a pH of 2.4, the mobile phase (5 mM H_3PO_4 and 1.5 mM tetrabutylammonium hydrogen sulphate) was filtered for 20 min from the column at 0.7 ml/min. The peaks were obtained at 205 nm. By calculating these peaks with ChemStation software, the values were obtained (Marklund et al. 2000).

Determination of xanthine oxidase activity

The plasma eluate, which was rich in protein, was incubated with 100 µM of xanthine at 37°C. Then, according to the difference in UA amounts, end-point analysis was conducted (Liu et al. 2003). For UA measurement, the same column and HPLC method were employed. For this purpose, blind tubes were prepared for each sample, and these were filled with 900 µl of eluate. Then, 100 µl of 1 mM xanthine (Sigma X-7375) was added to the sample tubes to perform the reaction. After this, both tubes were kept in a 37°C water bath for 30 min. Then, 100 µl of 1 mM xanthine was immediately added to the blind tube and, without delay, the reaction was stopped by placing both the sample and control tubes in boiling water for 5 min. Then, the tubes were centrifuged at 10,000 × g for 10 min, and 500 µl of supernatant was removed; UA measurements were performed, via the HPLC method. The XOA level was measured as the difference in UA concentration between the sample and blind tubes as plasma/min µmol UA (µmol/min/litre).

Determination of plasma nitrite

Nitrogen dioxide (NO_2) measurement was performed with an Apollo 2000 (WPI Instruments, Sarasota, FL, USA). The measurement was based on the permeability of the NO electrode to nitric oxide, which was electrochemically formed as a result of the reaction of NO_2 with KI and H_2SO_4 in an acidic medium (Zhang and Broderick 2000). Using 300 µl of plasma filtrate, it was possible to determine the plasma NO_2 amounts.

Statistical assessment

Before the experiment, to avoid making type-II errors (false negatives), the sample size was calculated using the GraphPad StatMate 2.0 (Windows 7) software (GraphPad Software Inc., San Diego, CA, USA) with the following parameters: alpha, 0.05; beta, 0.2; and power, 0.8. After the experiment, post hoc power analysis was performed using the same software. GraphPad Prism 6.0 (Windows 7) software (GraphPad Software Inc.) was used for statistically evaluating values gathered in the experiments. The values from the control and PE pregnant women were assessed via a Wilcoxon matched-pairs test. A Pearson correlation test was also performed. A z value which could be used to assess the significance of the difference between the two correlation coefficients was calculated using the Fisher r-to-z transformation. Then, the p value was found from the z value.

Results

The women were in 25–34 weeks' gestation (PE = 30.60 ± 3.8, control = 29.55 ± 3.27; mean ± standard deviation [SD]). The ages of the pregnant women ranged from 21 to 39 (PE = 29.65 ± 6.60, control = 27.75 ± 4.69; mean ± SD) years. Six of the PE patients had mild PE, and other 14 had severe conditions.

In Table I, the UA, XOA, allantoin and nitrite levels and the DBP, SBP and MAP values of the control and PE groups are given. The UA, XOA and allantoin levels, and DBP, SBP and MAP values of the PE patients were found to be higher when compared with those of controls. There were no statistical differences in terms of nitrite levels between the two groups.

In Table II, the correlations between the UA, XOA and allantoin levels and the SBP, DBP and MAP values of the subjects are given. The coefficients of correlation (r) and the significance levels (p) are reported in the table. In addition, a scatter plot with

Table I. The UA, XOA, allantoin, and nitrite levels of the control and PE groups and their SBP, DBP and MAP values. The results are given as arithmetic average ± SD.

	Control	PE	*p*
UA (μM)	233 ± 51	379 ± 64	< 0.0001
XOA (μM/min/litre)	0.25 ± 0.13	0.49 ± 0.22	< 0.0001
Allantoin (μM)	23.5 ± 5.87	35.5 ± 12.8	< 0.0001
Nitrite (μM)	3.72 ± 1.58	4.14 ± 1.75	0.43
SBP (mmHg)	116 ± 6.05	172 ± 15.5	< 0.0001
DBP (mmHg)	72.3 ± 8.19	107 ± 7.97	< 0.0001
MAP (mmHg)	86.7 ± 6.07	129 ± 9.42	< 0.0001

the regression line of the parameters in the PE group is given in Figure 1. According to the findings, there was no correlation between the UA, XOA and allantoin levels and BPs in the controls. On the other hand, our research showed strong evidence that there is a high level of correlation among PE patients' XOA, UA and allantoin levels and DBP, SBP and MAP values. The correlations of UA and allantoin with MAP were very high and very close to one another. There was no correlation between nitrite levels and BPs in either group.

The correlations of allantoin, UA and XOA with BP were compared statistically, and the significance of the differences between pairs of correlation coefficients is shown in Table III. In double-part comparisons, no statistical difference was observed between the correlations of UA, XOA and allantoin with SBP, DBP and MAP.

The aim of this study was to investigate whether UA, XOA and allantoin levels may be used to diagnose PE, and to determine the diagnostic superiority among them, using ROC analysis. The ROC curves are illustrated in Figure 2, while the areas, standard errors, *p* values, likelihood ratios and cut-off values which were determined from ROC analyses are given in Table IV. According to the results we obtained, XOA has the highest predictive value. Moreover, the predictive values of XOA and UA were significantly higher than that of allantoin (Table V). There was no statically significant difference between XOA and UA in terms of prediction of PE.

Discussion

The purpose of this study was to determine whether there are relationships between UA, XOA, allantoin and nitrite levels and BP, and to evaluate the diagnostic values of these parameters. According to the data we obtained, allantoin, UA and XOA levels were found to be high in relation to BP and were identified as good diagnostic predictors in cases of PE. However, the relationship between allantoin and PE was not stronger than the relationship between UA or XOA and PE. The level of nitrite did not increase in PE cases, and did not appear to have a relationship with BP.

In our study, the fact that the UA and XOA levels increased in cases of PE confirmed the results of previous studies (Karabulut et al. 2005; Redman et al. 1976; Sagen et al. 1984; Yildirim et al. 2004). In previous studies, the increase in UA and XOA levels in PE patients was considered to be connected to insufficient trophoblastic activity during PE (Reister et al. 1999). When trophoblastic activity decreases, placental cell death (apoptosis) is observed (He et al. 2013). Together with such cell deaths, there is an increase in genetic material degradation. Genetic material degradation results in an increase in the catalyst enzyme XO and end-product UA.

In essential (primary) hypertension patients, it has been claimed that UA and XOA levels are related to the severity of hypertension (Feig et al. 2008; Loeffler et al. 2012; Newaz et al. 1996). The increases in UA and XOA levels were considered to be connected with oxidative stress events, and the responsible agent was shown to be the increase in oxygen radicals due to XOA increase. It was also claimed that by suppressing XOA with allopurinol, BP could decrease. If this situation is like the stated condition in essential hypertension, it could also be valid for PE. The mechanism in the previous studies may be possible because UA and XOA increased over the natural course of PE. In our study, we found a high level of positive correlation between UA and XOA and BP in PE patients. Thus, our findings supported this idea.

According to our results, in terms of UA and XOA, if UA and XO levels have not increased in a hypertensive pregnant woman, a disease other than PE may be present. This idea has been described as disputable in previous studies. In two systematic reviews published in 2006, serum UA level was found to be a poor predictor of PE and its complications (Cnossen et al. 2006; Thangaratinam et al. 2006). However, a meta-analysis by Koopmans et al. (2009) found that UA is useful in predicting maternal complications and assisting in the management of PE. Johnson et al. (2011) also suggested that the measurement of serum UA is clinically useful and should be part of the evaluation of pregnant patients with hypertension, specifically in the primiparous patient after 20 weeks' gestation.

Another idea in our study is that allantoin level may have a relationship with BP in cases of PE. In addition, this relationship may be stronger than the relationship between UA or XOA and BP. This is because allantoin appears to replace UA under oxidative stress conditions. Since the level of UA and oxidative stress are greater in cases of PE, a greater increase in allantoin than UA seems to make sense. In this study, the allantoin levels in the plasma of PE patients were high, just as we expected. Again, allantoin has a strong relationship with BP in PE. According to these results, if the UA level is important in PE diagnosis and prognoses, as Koopmans et al. (2009) and Johnson et al. (2011) claim, the allantoin level may be useful in the same way. However, in the comparison test, the correlations of allantoin with BP were not superior to the correlations of UA and XOA with BP. In addition,

Table II. The correlations between the UA, XOA and allantoin levels in the control and PE groups and their SBP, DBP and MAP values. The correlation coefficients (*r*) and significance levels (*p*) are given.

	Control						PE					
	DBP		SBP		MAP		DBP		SBP		MAP	
	r	*P*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
UA	0.15	0.54	0.29	0.22	0.23	0.33	0.49	0.029	0.63	0.003	0.62	0.0036
XOA	0.05	0.84	0.10	0.67	0.08	0.74	0.47	0.039	0.37	0.11	0.47	0.038
Allantoin	− 0.08	0.73	0.16	0.50	− 0.02	0.93	0.58	0.0072	0.55	0.013	0.63	0.0031
Nitrite	− 0.14	0.56	− 0.09	0.71	− 0.16	0.51	− 0.12	0.61	0.31	0,19	0,10	0,67

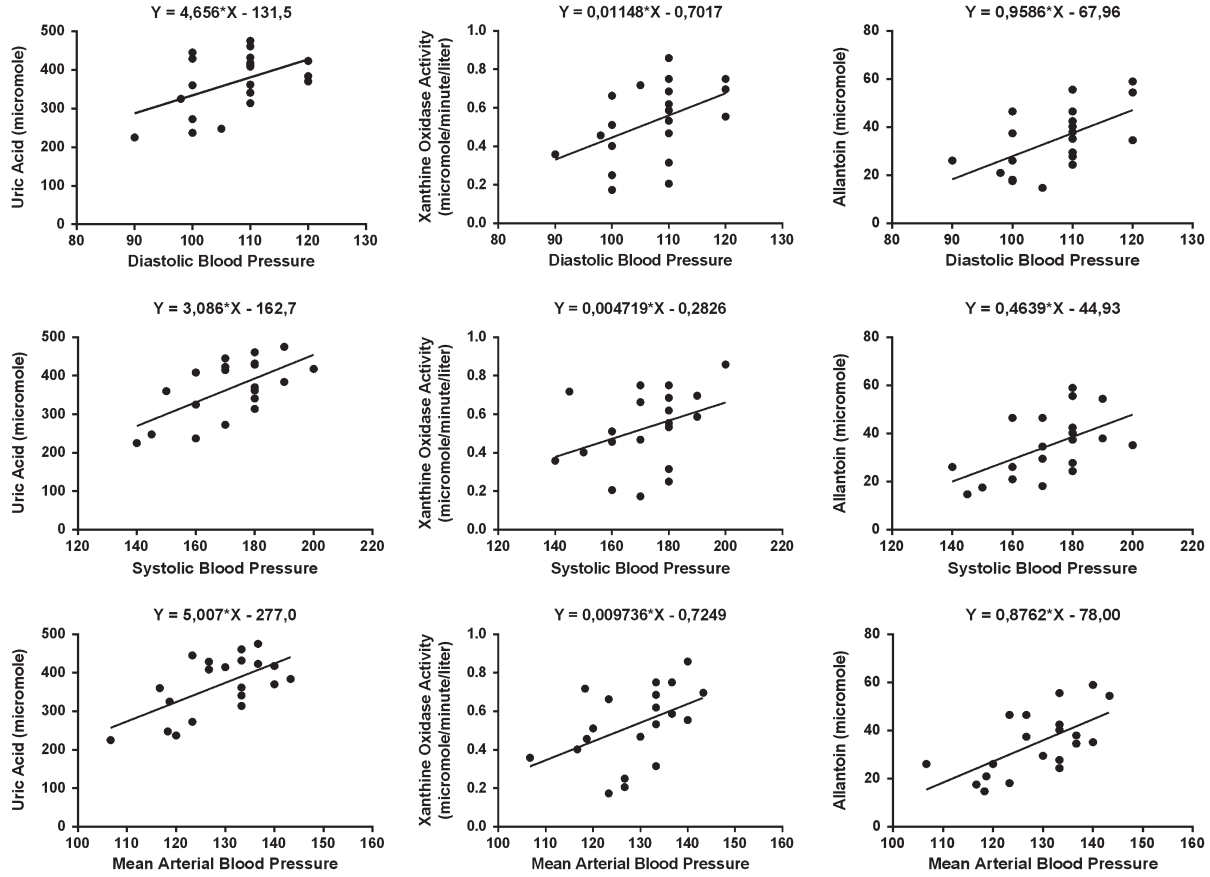

Figure 1. Scatter plot with regression line of the relationship among UA, XOA and allantoin values in the PE group and their SBP, DBP and MAP values.

in ROC analysis, allantoin was a poorer predictor of PE than UA and XOA. Thus, XOA seems to be the best predictor for PE.

A further thought in our study is that NO, which is dependent on XOA, will become oxidised to nitrite, thereby resulting in an increase in the amount of nitrite. According to the results we obtained, XOA increases in PE cases, whereas the level of nitrite did not increase. There was not a correlation between nitrite level and BP, which was in accordance with this result. It is possible that the lack of increase in nitrite levels in PE is related to the proper functioning of production/elimination balance. Perhaps the increasing effect of the XO enzyme on nitrite may not be clear in in vivo conditions, which is contradicts the claims of some other studies (Lundberg et al. 2008).

Table III. Significance of the difference between correlation coefficients (UA, XOA and allantoin levels and SBP, DBP and MAP values) in PE patients. *P* value is given.

	DBP	SBP	MAP
UA × XOA	0.94	0,31	0.52
UA × Allantoin	0.70	0.71	0.97
Allantoin × XOA	0.65	0.52	0.50

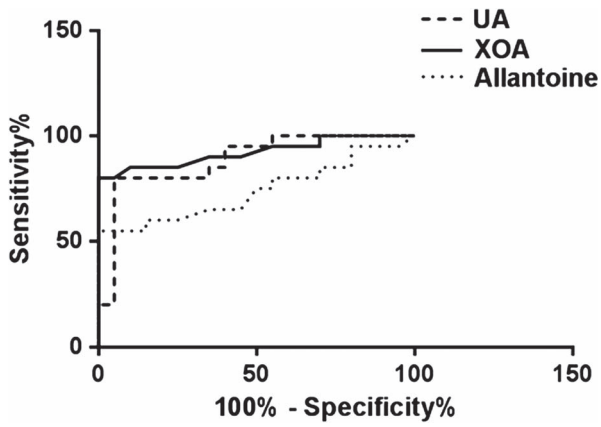

Figure 2. ROC curves of the UA, XOA and allantoin levels.

Our study has some weaknesses. We obtained data after PE had developed in patients. Although our data are enough to give us an opinion regarding the aim of our research, we could not determine whether these data are sufficient for early diagnosis, because the UA, XOA, allantoin and nitrite levels of all patients before the appearance of PE symptoms are unknown. In order to perform such an analysis and conduct the relevant study (if we accept that the minimum incidence of PR is 7%), we would need 300 patients. Moreover, because most patients were transferred to other centres, we could not perform a prognosis follow-up for the disease. In addition, we could not determine gestational age at delivery and birth weight of all the pregnant women. As a consequence, we obtained the best data that we could for our study and commented on them. Our study may be considered to be a pre-study for future long-term research in which blood samples will be taken before PE symptoms appear and the prognoses are followed up.

In the literature, we have not encountered a study that fully examined the relationship of UA, XOA, allantoin and nitrite with BP in cases of PE and that examined allantoin or nitrite levels in PE patients. According to the results found, if there is a strong relationship between BP and UA, XOA or allantoin in a pregnant

Table IV. ROC analysis results for the UA, XOA and allantoin levels.

	UA	Allantoin	XOA
Area	0.8850	0.7388	0.9213
Standard error	0.0548	0.0822	0.0456
95% Confidence interval	0.7776–0.9924	0.5777–0.8998	0.8319–1.011
P value	<0.0001	0.0098	<0.0001
Likelihood ratio	16	11	16
Cut-off value	310 (μM)	32.9 (μM)	0.321 (μM/min/litre)

Table V. Significance of the difference between the areas under two independent ROC curves.

	UA vs. Allantoin	Allantoin vs. XOA	XOA vs. UA
P value	0.0044	0.0002	0.2963

UA, uric acid; XOA, xanthine oxidase activity.

woman with hypertension, this patient may have PE. However, to support this claim, larger groups of pregnant women are needed. We hope that the answer to this question will be provided in future studies.

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