Serum Soluble Urokinase Plasminogen Activator Receptor Levels in Resistant Hypertension

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ABSTRACT

Background: Although the precise pathogenetic mechanisms remain incompletely elucidated, hypertension is characterized by endothelial damage and inflammation. The soluble urokinase plasminogen activator receptor (suPAR) is an inflammatory biomarker that increases in parallel with disease activity in conditions such as systemic inflammation, infection, cancer, and atherosclerosis. The objective of this study was to assess inflammation by means of serum suPAR levels in hypertensive patients and those with resistant hypertension.

Methods: Eighty-six adults, 29 newly diagnosed hypertensive patients (HT group) and 23 resistant hypertensive patients (RHT group) and 34 healthy controls, were included in this cross-sectional, observational study. Ambulatory blood pressure monitoring results were included in the analysis. Serum suPAR levels were measured using Enzyme-Linked ImmunoSorbent Assay (ELISA). Patients were divided into 2 groups as “high suPAR” and “low suPAR.”

Results: The serum suPAR level was lower in the control group than that of the HT and RHT groups (P = .001). Systolic and diastolic blood pressure values were positively correlated with the serum suPAR level (r = 0.254, P = .018; r = 0.239, P = .027, respectively). Being in the high-suPAR group was found to increase the risk of RHT by 19.5 times. Other risk factors for RHT were found to be lower urinary sodium excretion and higher urinary albumin excretion [odds ratio (OR) = 0.98; OR = 1.09, respectively].

Conclusion: In our study, suPAR levels were found associated with RHT. To our best knowledge, this study is the first to evaluate the relationship between serum suPAR levels and RHT.

Keywords: Endothelial damage, hypertension, inflammation, natriuresis, resistant hypertension, suPAR

INTRODUCTION

Hypertension (HT) is the most important major modifiable risk factor for cardiovascular events. Although HT awareness has increased in recent years, the rate of patients who can reach target blood pressure (BP) values with treatment remains between 35% and 50%.1,2 It is well known that cardiovascular mortality remarkably increases in patients whose BP is not within the target range. However, the risk of cardiovascular events is reportedly much higher among patients with high BP despite optimal therapy.3 This process, called resistant hypertension (RHT), is defined as “inability to control BP despite use of antihypertensive agents from at least 3 different classes, one of which is a diuretic, taken in appropriate combinations and at maximally tolerated doses, or to achieve BP control with at least 4 antihypertensives.”1,3 According to this definition, the reported prevalence of RHT is around 13% among HT patients under treatment. In the RHT population, the rate of patients whose BP is under control with 4 drugs has been reported as 30%.5 Therefore, the rate of RHT in the HT patient population is considerably high, and
Understanding the pathogenetic mechanisms of the disease is paramount for effective treatment.

Urokinase plasminogen activator receptor (uPAR), a key component of the fibrinolytic system, is a transmembrane protein expressed by vascular endothelial cells, immune system cells, mesenchymal cells, neurons, and glomerular and tubular epithelial cells. Its soluble form, suPAR, has potent proinflammatory and chemotactic properties with highly stable serum levels. It has been reported that serum suPAR levels are elevated in acute inflammatory processes, such as sepsis, systemic infection, and malignancy, as well as in chronic inflammatory processes, such as diabetes, glomerulosclerosis, and cardiovascular disease.9-11 A limited number of studies on the relationship between serum suPAR levels and HT have indicated higher suPAR levels in HT patients than in the healthy population.9,11

The present study investigates suPAR levels as an early marker of subclinical inflammation in patients with newly diagnosed HT and evaluates serum suPAR levels in RHT where more severe endothelial damage and inflammation are expected.

MATERIAL AND METHODS

Patient Selection and Data Collection

Eighty-six adults, consisting of 29 newly diagnosed HT patients (HT group) and 23 RHT patients (RHT group) and 34 healthy controls, were included in this cross-sectional, observational study. Exclusion criteria were age under 18 and presence of secondary HT, pregnancy, chronic drug use with the exception of RHT group, acute infection, active infection, acute kidney injury, coronary artery diseases, cerebrovascular disease, chronic kidney disease, chronic liver disease, connective tissue disease, chronic obstructive pulmonary disease, or malignancy. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Tekirdağ Namık Kemal University Medical Faculty (research protocol no. 2021.270.11.14; approval dated 03.12.2021). All subjects provided written informed consent.

Patients were asked to collect 24-hour urine during 24-hour ambulatory BP monitoring (ABPM). Sodium excretion rate and albuminuria were calculated from the 24-hour urine specimens.

Peripheral blood samples were collected in the morning following at least 8-hour fasting. Serum specimens obtained by centrifuging the blood samples at 2500 × g for 10 minutes were stored at −80°C. Serum suPAR levels were measured using a Bioassay Technology Laboratory (Shanghai Korain Biotech Co. Ltd., Shanghai, China) commercial ELISA kit (catalog no. E3759Hu; sensitivity 3.82 ng/L; intra-assay coefficient of variation (CV) < 8%; inter-assay CV < 10%).

The Measurement of Blood Pressure

Office BP monitoring was performed to diagnose HT, and measurements were interpreted in accordance with the ESC/ESH 2018 guideline recommendations.1 Office BP was measured using a UA-651SL monitor (A & D Company,1-243 Asahi, Kitamoto-shi, Saitama-ken, 364-8585 Japan), a validated device. The procedure was performed according to the “2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement.”12 In those in whom office measurements were compatible with the presence of HT, the diagnosis was confirmed by ABPM. A Mobil-O-Graph NG 24-hour ABPM Classic (I.E.M. GmbH, Stolberg, Germany) device was used for 24-hour ABPM measurement.

The BP measurement procedure applied in this study was also used in previous studies of our clinic.13,14

Definition of Resistant Hypertension

Patients failing to achieve target BP values despite using at least 3 antihypertensives, 1 a diuretic, at the maximum doses and in appropriate combinations were regarded as having RHT [1]. Detailed histories were taken from all patients, including dietary habits, drugs or substances used, and sleep habits. Patients with pseudo-resistant HT and secondary HT were excluded from the study.

Statistical Analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) 25.0 for Windows software (IBM SPSS Corp.; Armonk, NY, USA). Variable distributions were assessed using the Kolmogorov–Smirnov normality test. Comparison of continuous variables between 2 groups was performed using the independent-samples t test or Mann–Whitney U test based on the normality test results. Categorical variables were compared using the chi-square test. Correlation between 2 continuous variables was assessed using Pearson or Spearman correlation coefficients. The suPAR and body mass index (BMI) data were grouped due to their wide distribution ranges. The median suPAR value of the study group was 506.3 ng/L. Patients were...
divided into 2 groups based on this median value as “high-suPAR” and “low-suPAR.” The study group was divided into 2 groups based on the reference value of BMI, which is 30 kg/m², as “obese” and “non-obese.” Multinomial logistic regression analysis was applied to determine risk factors for HT and RHT [serum suPAR status, age, gender, obesity, systolic BP (SBP) and diastolic BP (DBP), urinary albumin and sodium excretion rates, serum creatinine, and uric acid]. Multivariate analysis was adjusted for confounders, which were found to be associated with HT and RHT in univariate analysis. Data are expressed as mean ± SD or median (minimum–maximum). \( P \) values less than .05 were regarded as statistically significant.

**RESULTS**

**Baseline Characteristics**

The mean age of the entire study group was 54.1 ± 8.2 years, and 46% of the participants were male. The mean BMI of the entire study group was 30.5 ± 5.6 kg/m². The distribution of the gender was similar between the groups. The age, BMI, serum uric acid level, and albuminuria were higher in RHT group. Twenty-four hour Na excretion rate was higher in the control group.

The serum suPAR level was lower in control group than that of the HT and RHT group (467.5 vs. 498.4 ng/L, \( P = .009 \) and 467.5 vs. 550.3 ng/L, \( P = .001 \), respectively). Patients’ demographic characteristics and laboratory findings of the study groups are shown in Table 1.

**Relationship Between Serum Soluble Urokinase Plasminogen Activator Receptor Level and Other Parameters**

When correlation analysis was performed across the entire study group, mean SBP and DBP values were positively correlated with the serum suPAR level (\( r = 0.254, P = .018; r = 0.239, P = .027 \), respectively).

| Table 1. Demographic Characteristics and Laboratory Findings of the Study Population |
|----------------------------------------|-------------------|-------------------|-------------------|--------|
|                                       | Control (n = 34)   | HT (n = 29)        | RHT (n = 23)       | \( P \) |
| Age (years)                           | 54.5 ± 5.7        | 50.7 ± 6.9         | 57.8 ± 11.0        | .006   |
| BMI (kg/m²)                           | 28.4 (19.2-39.9)  | 29.3 (20.0-49.8)   | 33.0 (25.8-45.0)   | .009   |
| Gender (male), n (%)                  | 20 (58.8%)        | 10 (34.5%)         | 10 (43.5%)         | .146   |
| SBP (mmHg)                            | 115.0 ± 11.6      | 132.5 ± 12.7       | 143.0 ± 12.9       | .000   |
| DBP (mmHg)                            | 70.7 ± 6.5        | 83.8 ± 9.9         | 83.9 ± 9.1         | .000   |
| Antihypertensive, n (%)               | –                 | –                 | –                 | –      |
| ACE-I                                 | –                 | –                 | 8 (34.8%)          | –      |
| ARB                                   | –                 | –                 | 15 (65.2%)         | –      |
| Diuretic                              | –                 | –                 | 23 (100%)          | –      |
| CCB                                   | –                 | –                 | 19 (82.6%)         | –      |
| Beta-blocker                          | –                 | –                 | 19 (82.6%)         | –      |
| Alpha-blocker                         | –                 | –                 | 5 (21.7%)          | –      |
| Glucose (mg/dL)                       | 101.5 (79-109)    | 101 (79-108)       | 114 (87-179)       | .072   |
| Creatinine (mg/dL)                    | 0.82 (0.53-1.06)  | 0.77 (0.64-1.45)   | 0.80 (0.52-1.29)   | .778   |
| Uric acid (mg/dL)                     | 4.9 ± 1.2         | 4.9 ± 1.2          | 6.0 ± 1.7          | .008   |
| Triglyceride (mg/dL)                  | 167 (67-512)      | 205 (85-681)       | 185 (61-350)       | .466   |
| Cholesterol (mg/dL)                   | 183.7 ± 40.8      | 199.8 ± 41.2       | 207.3 ± 51.3       | .132   |
| LDL (mg/dL)                           | 105.2 ± 30.8      | 113.3 ± 36.1       | 117.4 ± 34.2       | .405   |
| HDL (mg/dL)                           | 36 (23-77)        | 41 (23-75)         | 45 (30-67)         | .158   |
| UNaE (mEq/day)                        | 254.8 ± 113.0     | 188.5 ± 94.8       | 180.6 ± 106.4      | .013   |
| UAE (mg/day)                          | 6.4 (0.28-3)      | 6.0 (20-49.8)      | 155 (0-676)        | .000   |
| suPAR (ng/L)                          | 467.5 (252.8-843.2) | 498.4 (299.7-852.9) | 550.3 (415.8-882.4) | .001   |

Continuous variables are reported as mean ± SD or median (minimum–maximum) and categorical variables are reported as n.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, Calcium channel blocker; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; RHT, resistant hypertension; SBP, systolic blood pressure; suPAR, soluble urokinase plasminogen activator receptor; UAE, urinary albumin excretion rate; UNaE, urinary sodium excretion rate.
Determinants of Hypertension and Resistant Hypertension

Univariate and multivariate multinominal logistic regression analyses including biochemical and clinical parameters were performed across the entire study group. Twenty-four-hour Na excretion rate was found to be reversely associated with HT and RHT (odds ratio (OR) = 0.99; OR = 0.98, respectively). While being in the high-suPAR group was found to be a risk factor for RHT (OR = 19.49, \( P < .001 \)), it was not found to be associated with HT. Also albuminuria was associated with RHT (OR = 1.09) (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study investigating serum suPAR levels in patients with RHT. Serum suPAR levels were similar in the HT and RHT groups, whereas they were significantly lower in the healthy control group. On the other hand, the level was higher in the RHT than in the HT group, though it was statistically insignificant. Besides, SBP and DBP values were positively correlated with serum suPAR levels. Being in the high-suPAR group was found to increase the risk of RHT by 19.5 times, while it was not found to be significant in terms of HT.

The results of most studies on the correlation between suPAR level and cardiovascular prognosis support the view that serum/plasma suPAR level can be used as a new risk marker. Published literature includes various studies on the association between serum suPAR level and cardiovascular risk profile, but studies investigating this relationship only in terms of HT are scarce. In a study on black individuals, Botha et al have reported a higher increase in serum suPAR levels in normotensive individuals who developed HT over 5 years, and SBP correlated positively with baseline serum suPAR in the same patient group. It is unclear whether high suPAR levels in cardiovascular diseases are indicative of pathogenesis or HT-related inflammatory response. It has been suggested that vascular injury mediated by plasminogen activator inhibitor-1 (PAI-1) and its receptor, uPAR, may result in HT due to impairment of endothelial function, decreased endothelial nitric oxide synthase (eNOS) level, and, thus, reduced vasodilator response. On the other hand, hypertensive vascular changes creating a prothrombotic environment through endothelial and platelet dysfunction may lead to an increase in the elements of plasminogen-to-plasmin cascade and hence in the level of serum suPAR.

Table 2. Logistic Regression for Hypertension Status in the Study Population

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>B</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>0.029</td>
<td>1.03 (0.38-2.79)</td>
</tr>
<tr>
<td>High suPAR</td>
<td>0.806</td>
<td>2.24 (0.79-6.32)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.037</td>
<td>0.96 (0.66-1.41)</td>
</tr>
<tr>
<td>UNaE</td>
<td>-0.006</td>
<td>0.99 (0.99-1.00)</td>
</tr>
<tr>
<td>UAE</td>
<td>0.019</td>
<td>1.02 (0.98-1.06)</td>
</tr>
<tr>
<td><strong>Resistant Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1.278</td>
<td>3.59 (1.14-11.34)</td>
</tr>
<tr>
<td>High suPAR</td>
<td>2.434</td>
<td>11.40 (3.09-42.1)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.561</td>
<td>1.75 (1.14-2.70)</td>
</tr>
<tr>
<td>UNaE</td>
<td>-0.007</td>
<td>0.99 (0.99-1.00)</td>
</tr>
<tr>
<td>UAE</td>
<td>0.047</td>
<td>1.05 (1.01-1.09)</td>
</tr>
</tbody>
</table>

OR, Odds ratio; (with 95% confidence interval), BMI, Body mass index; suPAR, Soluble urokinase plasminogen activator receptor; UNaE, Urinary sodium excretion; UAE, Urinary albumin excretion.
higher suPAR levels in the RHT patient group but obtained no statistical difference between the HT and RHT groups in this respect. On the other hand, being in the high-suPAR group was found to increase the risk of RHT by 19.5 times. We think that this may be due to the small size of our study population.

Obesity is considered a major cardiovascular risk factor. Factors such as RAAS activation, sympathetic nervous system activation, decreased natriuretic peptide level, decreased leptin level, and increased kidney compression due to elevated intra-abdominal pressure have been held responsible for the relationship between obesity and HT. Available information on the link between the development of HT and obesity is contradictory. Obesity is common in the RHT population. In the present study, although the mean BMI was higher in the RHT group compared to the other groups, no correlation was found between obesity and HT and RHT.

Uric acid has been reported to play a role in the pathogenesis and complications of cardiovascular disease through various mechanisms. In our study, serum uric acid level was higher in the RHT group compared to the other groups. Univariate analysis revealed a relationship between serum uric acid level and HT and RHT, but this was not confirmed by multivariate analysis. The use of thiazide by all patients in the RHT group may explain the high serum uric acid level in this group.

Studies have also shown that a high-salt diet plays a key role in the risk of developing HT, particularly in salt-sensitive individuals. Angiotensin II and sympathetic nervous system activation lead to increased kidney tubular sodium reabsorption and, thus, a decreased urinary sodium excretion rate. Individuals with RHT are typically salt sensitive. In our study, urinary sodium excretion rate was higher in the normotensive group than in the other 2 groups. Besides, there was a correlation between low urinary sodium levels and HT and RHT.

We observed significantly higher albuminuria levels in the RHT group than in the other groups. This may be explained by the higher risk of end-organ damage and more prominent RAAS activation in RHT prognosis.

A limitation of our study is the small patient population. However, coronary artery disease often accompany RHT, and it is difficult to find patients without these comorbidities. Another limitation is that all patients in the RHT group were using RAAS-blocking drugs. This may have been the reason why the difference in serum suPAR levels between the RHT and the HT group was not statistically significant. Nevertheless, considering patient health and ethical issues, the drugs could not be discontinued.

To conclude, being in high-suPAR group was determined to be associated with RHT. We observed higher suPAR levels in the RHT patient group but obtained no statistical difference between the HT and RHT groups. Obtaining more data on the pathogenesis of RHT, where end-organ damage is more severe, will contribute to better management of the process. Based on the relationship between MRs, ENaC, and the plasminogen-to-plasmin cascade, we think that the role of suPAR in HT and RHT deserves to be examined in greater detail.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of Tekirdağ Namık Kemal University Medical Faculty (research protocol no. 2021.270.11.14; approval dated 03.12.2021).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.


**Declaration of Interests:** The authors have no conflict of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

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