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Original Article

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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 ImmonuSorbent 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

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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%.[4] 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.[5-8] 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, 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

MAIN POINTS

- The serum soluble urokinase plasminogen activator receptor (suPAR) level was found to be lower in the healthy group compared to the hypertensive group.
- Although the serum suPAR level was high in the resistant hypertension (RHT) group, the difference between RHT and hypertension groups was not significant.
- When patients were divided into 2 groups based on the median value of the serum suPAR level, being in the high-suPAR group was found to increase the risk of RHT by 19.5 times.
- Based on the relationship between the plasminogen-to-plasmin cascade and the mineralocorticoid receptor and epithelial sodium channel pathways, which are suggested to be involved in the pathogenesis of resistant hypertension, it seems possible that the serum suPAR level is among the markers of this process.

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/m^2, as "obese" and "non-obese." Multinominal 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/m^2. 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/m^2)	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.

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

	Univariate			Multivariate		
Covariates	**B**	**OR**	***P***	**B**	**OR**	***P***
Hypertension						
Obesity	0.029	1.03 (0.38-2.79)	.955	-0.114	0.89 (0.28-2.82)	.846
High suPAR	0.806	2.24 (0.79-6.32)	.127	0.850	2.34 (0.74-7.43)	.150
Uric acid	-0.037	0.96 (0.66-1.41)	.849	-0.148	0.86 (0.55-1.35)	.519
UNaE	-0.006	0.99 (0.99-1.00)	.022	-0.008	0.99 (0.99-1.00)	.012
UAE	0.019	1.02 (0.98-1.06)	.369	0.039	1.04 (0.99-1.09)	.100
Resistant Hypertension						
Obesity	1.278	3.59 (1.14-11.34)	.030	1.667	5.30 (0.62-45.04)	.127
High suPAR	2.434	11.40 (3.09-42.1)	< .001	2.970	19.49 (2.10-180.56)	.009
Uric acid	0.561	1.75 (1.14-2.70)	.011	-0.132	0.88 (0.36-2.13)	.771
UNaE	-0.007	0.99 (0.99-1.00)	.015	-0.019	0.98 (0.97-0.99)	.005
UAE	0.047	1.05 (1.01-1.09)	.026	0.084	1.09 (1.02-1.16)	.007

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.

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.[6,15,16] 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[10] 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.[10] 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.[17] 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.[11,18]

It is thought that the basic pathology in the development of HT is the deterioration of the physiological balance between kidney tubular sodium reabsorption and excretion, and mineralocorticoid receptors (MRs) play a key role in this process.[19] The 2 primary mediators associated with MR activation in HT and related end-organ damage are aldosterone- and amiloride-sensitive epithelial sodium channels (ENaC).[20,21] The 2 mediators are also reported to be crucial for RHT pathogenesis.[22-24] A close relationship was found between aldosterone and angiotensin II and the plasminogen-to-plasmin cascade. It has been shown that this relationship significantly contributes to the pathogenesis of kidney fibrosis due to various causes, including HT, and that renin–angiotensin–aldosterone system (RAAS) blockade regresses the levels of uPAR, suPAR, and PAI-1, a potent profibrotic molecule, and tissue fibrosis. [25-30] In addition to RAAS blockade, amiloride, an ENaC inhibitor, reportedly reduces uPAR levels and supports BP regulation in HT and RHT patients.[17,31] High suPAR levels are expected in RHT patients since severe inflammation and end-organ damage are likely. However, in our study, we observed

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.[32] 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.[33] Available information on the link between the development of HT and obesity is contradictory.[34] Obesity is common in the RHT population.[35] 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.[36,37] 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.[38,39] Angiotensin II and sympathetic nervous system activation lead to increased kidney tubular sodium reabsorption and, thus, a decreased urinary sodium excretion rate.[40,41] 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.[35]

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.

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REFERENCES

1. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. [CrossRef]
2. Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310(9):959-968. [CrossRef]
3. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72(5):e53-e90. [CrossRef]
4. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension*. 2011;57(6):1076-1080. [CrossRef]
5. Backes Y, van der Sluijs KF, Mackie DP, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review. *Intensive Care Med*. 2012;38(9):1418-1428. [CrossRef]
6. Eugen-Olsen J, Andersen O, Linneberg A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. *J Intern Med*. 2010;268(3):296-308. [CrossRef]
7. Persson M, Engström G, Björkbacka H, Hedblad B. Soluble urokinase plasminogen activator receptor in plasma is associated with incidence of CVD. Results from the Malmo diet and cancer study. *Atherosclerosis*. 2012;220(2):502-505. [CrossRef]

8. Wada T, Nangaku M, Maruyama S, et al. A multicenter cross-sectional study of circulating soluble urokinase receptor in Japanese patients with glomerular disease. *Kidney Int*. 2014;85(3):641-648. [CrossRef]
9. Luo S, Coresh J, Tin A, et al. Soluble urokinase-type plasminogen activator receptor in black Americans with CKD. *Clin J Am Soc Nephrol*. 2018;13(7):1013-1021. [CrossRef]
10. Botha S, Fourie CM, Schutte R, Eugen-Olsen J, Schutte AE. Soluble urokinase plasminogen activator receptor and hypertension among black South Africans after 5 years. *Hypertens Res*. 2015;38(6):439-444. [CrossRef]
11. Park MY, Herrmann SM, Saad A, et al. Biomarkers of kidney injury and klotho in patients with atherosclerotic renovascular disease. *Clin J Am Soc Nephrol*. 2015;10(3):443-451. [CrossRef]
12. Stergiou GS, Palatini P, Parati G, et al. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. *J Hypertens*. 2021;39(7):1293-1302. [CrossRef]
13. Bayrakci N, Ozkan G, Kara SP, Yilmaz A, Guzel S. Serum calprotectin level as an inflammatory marker in newly diagnosed hypertensive patients. *Int J Hypertens*. 2022;2022:6912502. [CrossRef]
14. Kara SP, Ozkan G, Yılmaz A, Bayrakçı N, Güzel S, Geyik E. MicroRNA 21 and microRNA 155 levels in resistant hypertension, and their relationships with aldosterone. *Ren Fail*. 2021;43(1):676-683. [CrossRef]
15. Hodges GW, Bang CN, Wachtell K, Eugen-Olsen J, Jeppesen JL. suPAR: A new biomarker for cardiovascular disease? *Can J Cardiol*. 2015;31(10):1293-1302. [CrossRef]
16. Botha S, Fourie CMT, Schutte R, Eugen-Olsen J, Pretorius R, Schutte AE. Soluble urokinase plasminogen activator receptor as a prognostic marker of all-cause and cardiovascular mortality in a black population. *Int J Cardiol*. 2015;184:631-636. [CrossRef]
17. Svenningsen P, Hinrichs GR, Zachar R, Ydegaard R, Jensen BL. Physiology and pathophysiology of the plasminogen system in the kidney. *Pflugers Arch*. 2017;469(11):1415-1423. [CrossRef]
18. Lyngbæk S, Sehestedt T, Marott JL, et al. CRP and suPAR are differently related to anthropometry and subclinical organ damage. *Int J Cardiol*. 2013;167(3):781-785. [CrossRef]
19. Fournier D, Luft FC, Bader M, Ganten D, Andrade-Navarro MA. Emergence and evolution of the renin-angiotensin-aldosterone system. *J Mol Med (Berl)*. 2012;90(5):495-508. [CrossRef]
20. Kusche-Vihrog K, Callies C, Fels J, Oberleithner H. The epithelial sodium channel (ENaC): mediator of the aldosterone response in the vascular endothelium? *Steroids*. 2010;75(8-9):544-549. [CrossRef]
21. Warnock DG, Kusche-Vihrog K, Tarjus A, et al. Blood pressure and amiloride-sensitive sodium channels in vascular and renal cells. *Nat Rev Nephrol*. 2014;10(3):146-157. [CrossRef]
22. Judd EK, Calhoun DA, Warnock DG. Pathophysiology and treatment of resistant hypertension: the role of aldosterone and amiloride-sensitive sodium channels. *Semin Nephrol*. 2014;34(5):532-539. [CrossRef]
23. Shibata H, Itoh H. Mineralocorticoid receptor-associated hypertension and its organ damage: clinical relevance for resistant hypertension. *Am J Hypertens*. 2012;25(5):514-523. [CrossRef]
24. Clark D, 3rd, Ahmed MI, Calhoun DA. Resistant hypertension and aldosterone: an update. *Can J Cardiol*. 2012;28(3):318-325. [CrossRef]
25. Knier B, Cordasic N, Klanke B, et al. Effect of the plasminogen-plasmin system on hypertensive renal and cardiac damage. *J Hypertens*. 2011;29(8):1602-1612. [CrossRef]
26. Kagami S, Kuhara T, Okada K, Kuroda Y, Border WA, Noble NA. Dual effects of angiotensin II on the plasminogen/plasmin system in rat mesangial cells. *Kidney Int*. 1997;51(3):664-671. [CrossRef]
27. Brown NJ, Agirbasli MA, Williams GH, Litchfield WR, Vaughan DE. Effect of activation and inhibition of the renin-angiotensin system on plasma PAI-1. *Hypertension*. 1998;32(6):965-971. [CrossRef]
28. Persson F, Theilade S, Eugen-Olsen J, Rossing P, Parving HH. Renin angiotensin system blockade reduces urinary levels of soluble urokinase plasminogen activator receptor (suPAR) in patients with type 2 diabetes. *J Diabetes Complications*. 2016;30(8):1440-1442. [CrossRef]
29. Brown NJ, Nakamura S, Ma L, et al. Aldosterone modulates plasminogen activator inhibitor-1 and glomerulosclerosis in vivo. *Kidney Int*. 2000;58(3):1219-1227. [CrossRef]
30. Ferreira JP, Verdonschot J, Wang P, et al. Proteomic and mechanistic analysis of spironolactone in patients at risk for HF. *JACC Heart Fail*. 2021;9(4):268-277. [CrossRef]
31. Oxlund CS, Buhl KB, Jacobsen IA, et al. Amiloride lowers blood pressure and attenuates urine plasminogen activation in patients with treatment-resistant hypertension. *J Am Soc Hypertens*. 2014;8(12):872-881. [CrossRef]
32. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *Circulation*. 2019;140(11):e596-e646. [CrossRef]
33. Chrysant SG. Pathophysiology and treatment of obesity-related hypertension. *J Clin Hypertens (Greenwich)*. 2019;21(5):555-559. [CrossRef]
34. Zhou W, Shi Y, Li YQ, et al. Body mass index, abdominal fatness, and hypertension incidence: a dose-response meta-analysis of prospective studies. *J Hum Hypertens*. 2018;32(5):321-333. [CrossRef]
35. Oliveras A, de la Sierra A. Resistant hypertension: patient characteristics, risk factors, co-morbidities and outcomes. *J Hum Hypertens*. 2014;28(4):213-217. [CrossRef]
36. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*. 2003;41(6):1183-1190. [CrossRef]
37. Ndrepepa G. Uric acid and cardiovascular disease. *Clin Chim Acta*. 2018;484:150-163. [CrossRef]
38. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt cooperative research group. *BMJ*. 1988;297(6644):319-328. [CrossRef]
39. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med*. 2014;371(7):601-611. [CrossRef]
40. Edwards A, McDonough AA. Impact of angiotensin II-mediated stimulation of sodium transporters in the nephron assessed by computational modeling. *Am J Physiol Ren Physiol*. 2019;317(6):F1656-F1668. [CrossRef]
41. DiBona GF. Physiology in perspective: the wisdom of the body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol*. 2005;289(3):R633-R641. [CrossRef]