The relationship between serum total testosterone and 24-hour urinary sodium excretion in never-treated stage 1 essential hypertensive patients

Hiç tedavi edilmemiş evre 1 esansiyel hipertansiyon hastalarında serum total testosteron düzeyi ve 24 saatlik idrar sodyum atılımı arasındaki ilişki

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ABSTRACT

Objectives: To study the relationship between serum total testosterone (TT) and 24-hour urinary sodium excretion in newly diagnosed stage 1 essential hypertensive patients with normal renal function.

Study design: In total, 80 never-treated stage 1 hypertensive patients were included. All patients provided medical history and underwent physical examination, blood pressure measurement, 12-lead electrocardiography, routine urine analysis, biochemical analysis, 24-hour urine collection to measure urinary sodium and protein excretion, and creatinine clearance calculation.

Results: Pearson correlation analysis revealed that logarithmically converted 24-hour urinary sodium excretion was correlated with age (r=-0.399, p<0.0001), body mass index, (r=0.304, p=0.006), systolic blood pressure (r=0.394, p<0.0001), serum potassium (r=0.233, p=0.037), creatinine clearance (r=0.600, p<0.0001), and logarithmically converted serum TT (r=-0.272, p=0.015). Stepwise linear regression analysis revealed that age (p<0.0001), creatinine clearance (p=0.015), systolic blood pressure (p<0.0001), potassium (p=0.021), and serum TT (p=0.002) were independently related to logarithmically converted 24-hour sodium excretion.

Conclusion: We demonstrated that serum TT levels were independently related to 24-hour urinary sodium amount.

ÖZET

Amaç: Hiç tedavi edilmemiş ve böbrek fonksiyonları normal olan evre 1 esansiyel hipertansiyon hastalarında serum total testosteron (TT) ve 24 saatlik idrar sodyum atılımı arasındaki ilişki değerlendirildi.

Çalışma planı: Çalışmaya 80 yeni tanı konmuş, hiç tedavi görmemiş, evre 1 hipertansif hasta alındı. Çalışmaya katılan hastaların tıbbi öyküleri alındı ve fizik muayeneleri, kan basıncı ölçümleri, 12 derivasyonlu elektrokardiyografik incelemeleri, idrar analizi ve biyokimyasal analizler yapıldı, 24 saatlik idrar toplanarak idrar sodyumu, idrar protein atılımı ve kreatinin klirensi hesaplandı.

Bulgular: Tek değişkenli Pearson korelasyon analizinde logaritmik olarak çevrilen 24 saatlik idrar sodyum atımı yaş (r=-0.399, p=<0.0001), beden kütle indeksi (r=0.304, p=0.006), sistolik kan basıncı (r=0.394, p<0.0001), potasyum (r=0.233, p=0.037), kreatinin klirensi (r=0.600, p<0.0001) ve logaritmik olarak çevrilen serum TT ile (r:-0.272, p=0.015) ilişkili bulundu. Çok değişkenli lineer regresyon analizinde yaş (p<0.0001), kreatinin klirensi (p=0.015), sistolik kan basıncı (p<0.0001), potasyum (p=0.021) ve serum TT (p=0.002) logaritmik olarak çevrilen 24 saatlik idrar sodyum atılımının bağımsız öngördürücüleri olarak bulundu.

Sonuç: Bu çalışmamızda, serum TT seviyelerinin 24 saatlik idrar sodyum atılımı ile bağımsız ilişkili olduğunu gösterdik.

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High blood pressure (BP) is a major public health problem and the most important preventable risk factor for stroke, cardiovascular and renal disease.[1] It is well known that the incidence and severity of hypertension is greater in men than in women.[2] Additionally, normotensive men typically exhibit higher BP than age-matched premenopausal women.[3] Although the mechanisms underlying the gender difference are unclear,[4] sex steroids have been previously shown to mediate salt sensitivity. For example, in women, BP becomes more salt-sensitive after menopause, suggesting that estradiol may protect against salt sensitivity.[5] Estradiol has been shown to down-regulate angiotensin type 1 receptor and angiotensin converting enzyme expression in the kidneys and in the brains of female normotensive rats.[6] In contrast, testosterone was previously shown to upregulate angiotensinogen in the kidneys of male spontaneously hypertensive rats (SHR) and to decrease sodium excretion[7,8] and mediate hypertension in several rat models, such as SHR.[9] Additionally, in male SHR, the presence of testosterone and androgen receptors through puberty is required for development of hypertension and associated sympathetic nervous system potentiation.[10,11]

Thus, in light of the above findings, we hypothesized that serum total testosterone (TT) levels are negatively associated with 24-hour urinary sodium excretion in hypertensive males.

The current study was conducted to test whether serum TT levels were associated with 24-hour urine sodium excretion in never-treated stage 1 essential hypertensive patients.

PATIENTS AND METHODS

The current study was conducted in the outpatient nephrology unit of Konya Numune State Hospital between August 2010 and July 2011. The study was in accordance with the Declaration of Helsinki, and local ethical approval and informed consent were obtained before enrollment. The study population consisted of male patients with newly diagnosed stage 1 hypertension that was hitherto treated. Patients with diabetes mellitus, coronary artery disease, heart failure, hypertensive urgency or emergency, rhythm problems, hypo- or hyperthyroidism, liver disease, nephrotic syndrome, or urinary tract infection were excluded. None of the patients reported any alcohol intake.

Abbreviations:

BMI	*Body mass index*
BP	*Blood pressure*
RAS	*Renin-angiotensin system*
SHR	*Spontaneously hypertensive rats*
TT	*Total testosterone*

All patients provided medical history and underwent the following: physical examination, body mass index (BMI) calculation, BP measurement, 12-lead electrocardiographic evaluations, urine analysis, biochemical analysis, 24-hour urine collection to measure urinary sodium and protein excretion, and creatinine clearance. An information leaflet and a urine container were given to all subjects. They also received verbal instructions on how to collect a proper 24-hour urine sample. During the sampling period, subjects were instructed to keep urine samples in a dark and cool place. The urine containers were brought to the laboratory within 2-4 hours of the end of the collection period. Since erroneous estimations of salt intake may occur due to problems with the collecting of 24-hour urine samples, participants with urinary creatinine outside of reference levels (the accepted reference intervals for 24-hour urinary creatinine were 10.7-26.0 g/kg for women and 12.1-28.9 g/kg for men) were excluded.[12]

Blood pressure measurement

Seated clinic BP was measured manually with a mercury column sphygmomanometer and an appropriate size cuff after five minutes of rest according to AHA (American Heart Association) guidelines.[13] Stage 1 hypertension was defined as systolic BP between 140-159 mmHg and diastolic BP between 90-99 mmHg.[14]

Laboratory analysis

Routine laboratory parameters were measured after 10-12 hours of fasting. Blood glucose, urea, creatinine, uric acid, sodium, potassium, hemoglobin, albumin, calcium, phosphorus, total cholesterol, low density lipoprotein cholesterol (LDL-cholesterol), high density lipoprotein cholesterol (HDL-cholesterol), triglycerides, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and TT levels were measured. Twenty-four-hour urinary Na and protein excretion were also measured.

The levels of fasting glucose, urea, creatinine, uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were determined using commercially available assay kits with an auto-analyzer (Architect® c16000, Abbott Diagnostics, Abbott Park,

Table 1. The demographic and laboratory parameters of patients

Parameter	Mean±SD
Age (years)	54.9±11.6
Body mass index (kg/m^2)	26.2±4.5
Smoker / Non-smoker (N)	23/57
Systolic blood pressure (mmHg)	144.1±8.3
Diastolic blood pressure (mmHg)	86.7±7.7
Serum glucose (mmol/L)	5.1±0.8
Serum urea (mg/dL)	33.1±15.3
Creatinine (μmol/L)	86.6±18.6
Hemoglobin (g/L)	135.3±23.1
Sodium (mmol/L)	140.2±3.9
Potassium (mmol/L)	4.57±0.67
Albumin (g/L)	43.2±3.1
Total cholesterol (mmol/L)	4.63±1.1
LDL-C (mmol/L)	2.49±0.73
HDL-C (mmol/L)	1.22±0.33
Triglyceride (mmol/L)	1.77±1.39
Uric acid (μmol/L)	422.3±129.1
Thyroid stimulating hormone (mU/L)	1.82±1.15
FT3 (pg/ml)	3.26±0.45
FT4 (ng/dl)	1.24±0.16
Total testosterone (nmol/L)	15.5±5.6
24-hour urine protein excretion rate	190.7±221.3
24-hour urinary sodium excretion	200.4±78.2
Creatinine clearance (ml/min)/1.73 m^2	84.0±16.6

SD: Standard deviation; LDL-C: Low-density lipoprotein cholesterol; HDL-C: Low-density lipoprotein cholesterol; FT3: Free triiodothyronine; FT4: Free thyroxine.

Illinois, USA). Hemoglobin was measured using an automated blood analyzer (CELL-DYN 3700 cell counter, Abbott Diagnostics Division, Abbott Laboratories, Illinois, USA). Serum sodium, serum potassium, and urine sodium were measured using the direct potentiometric method and ion-specific electrodes. Twenty-four-hour protein excretion was measured using the benzethonium chloride method (Architect® c16000, Abbott Diagnostics, Abbott Park, Illinois, USA). Albumin was measured using the bromcresol purple method. TSH, FT3, FT4, and TT were assayed using the direct chemiluminescence method (Advia Centaur XP, Siemens, Dublin, Ireland).

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Evanston, Illinois, USA). Results were considered statistically significant if the two-tailed *p* value was less than 0.05. Data were checked for normality. Pearson's correlation coefficient r was used for correlations. Linear regression analysis was performed to analyze the independent factors, including demographic factors (age, smoking status, BMI), systolic and diastolic BP, and laboratory parameters (sodium, potassium, albumin, 24-hour creatinine clearance and urine protein excretion, and total serum testosterone) related to logarithmically converted 24-hour urinary sodium excretion (as a dependent variable). A correlation was demonstrated between these independent parameters and 24-hour sodium excretion either in the present study, using univariate correlation analysis, or in the literature; all the parameters were, therefore, included.

RESULTS

Initially, 118 patients were enrolled. Four patients with hypothyroidism, one patient with hyperthyroidism, two patients with coronary artery disease, two patients with heart failure, three patients with hypertensive urgency/emergency, three patients with diabetes, two patients with chronic liver disease, two patients with nephrotic syndrome, two patients with atrial fibrillation, two patients with urinary tract infection, five patients who did not want to participate, and 10 patients with incomplete 24-hour urine calculations were excluded from the study. The final patient population consisted of 80 never-treated stage 1 hypertensive patients. Patient demographic and laboratory parameters are shown in Table 1.

Pearson correlation analysis revealed that 24-hour urinary sodium excretion was correlated with age (r=-0.399, p<0.0001), BMI (r=0.304, p=0.006), systolic BP (r=0.394, p<0.0001), serum potassium (r=0.233, p=0.037), creatinine clearance (r=0.600, p<0.0001), and logarithmically converted serum TT (r=-0.272, p=0.015; Fig. 1). Stepwise linear regression was performed on the independent factors, including age, smoking status, BMI, systolic BP, diastolic BP, serum sodium, potassium, albumin, 24-hour creatinine clearance and urine protein excretion, and total serum testosterone, related to logarithmically converted 24-hour sodium excretion (as a dependent parameter). The results of the linear regression revealed that age (p<0.0001), creatinine clearance (p=0.015), systolic

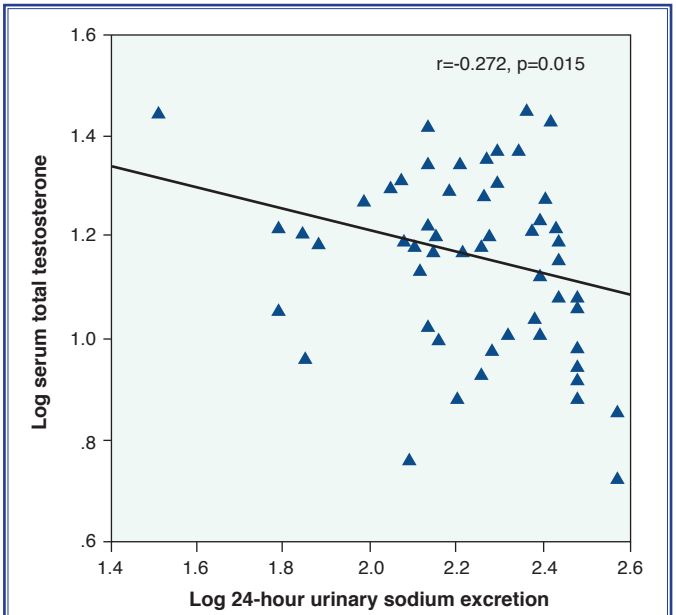

Figure 1. The scatter plot of the relationship between logarithmically-converted 24-hour urinary sodium excretion and logarithmically-converted serum total testosterone.

BP (p<0.0001), serum potassium (p=0.021), and serum TT (p=0.002) were independently related to logarithmically converted 24-hour sodium excretion (as a dependent parameter; Table 2).

DISCUSSION

In the current study, apart from the other factors, we demonstrated that serum TT levels were independently and negatively correlated with 24-hour urinary sodium excretion in never-treated newly diagnosed stage 1 essential hypertensive patients. To the best of our knowledge, our findings have not been previously demonstrated.

Over the last few decades, experimental, observational and clinical data have indicated that dietary salt intake is closely related to BP.[15] The INTERSALT study was the first worldwide epidemiological study in which a significant relation between 24-hour urinary Na excretion and BP was established.[16] Following INTERSALT, other epidemiological studies[17,18] and randomized controlled trials[19,20] have also detected a relation between elevated BP and high salt intake. Thus, reduction of salt intake has become a common sense approach to both prevention and amelioration of hypertension,[21] and various guidelines recommend lower daily sodium intake. The 2003 Seventh Joint National Committee guidelines recommend reducing dietary sodium intake to 100 mmol/day (6 g salt),[14] and the recent European Society of Hyperten-

Table 2. Stepwise linear regression analysis of factors related to logarithmically-converted 24-hour urinary sodium excretion

	B	β	95% CI	*p*
Age	-0.007	-0.366	-0.01-(-0.03)	**<0.0001**
Creatinine clearance	0.003	0.257	0.001-0.006	0.015
Systolic blood pressure	0.01	0.368	0.005-0.014	**<0.0001**
Serum potassium	0.061	0.188	0.01-0.113	0.021
Serum total testosterone	-0.009	-0.250	-0.015-(-0.004)	0.002

CI: Confidence interval.

sion recommends <85 mmol/day sodium intake for hypertensive patients.[22]

It is well known that the incidence and severity of hypertension is greater for men than for women.[2] Additionally, normotensive men typically exhibit higher BP than age-matched premenopausal women.[3] Although the mechanisms remain unclear, the role of sex steroids in sodium excretion may explain the discrepancy between males and females. Indeed, in previous studies, mechanisms have been proposed regarding the relationship between sex steroids and sodium excretion. In Dahl salt-sensitive rats, males exhibited greater salt sensitivity to hypertension than females.[23] It was shown that testosterone contributes to the development of hypertension and renal injury in male Dahl salt rats on a high salt diet, possibly through upregulation of the intrarenal renin-angiotensin system (RAS).[24] Additionally, androgens have been shown to stimulate sodium reabsorption by the proximal tubule in a RAS-dependent manner.[25] Thus, given these findings, one could speculate that the androgen-mediated increase in renal angiotensinogen, and the resulting increase in angiotensin II, could cause an increase in sodium reabsorption along the nephron and a decrease in 24-hour sodium excretion. However, no previous study has examined the relationship between testosterone levels and urinary sodium excretion in hypertensive subjects. Therefore, we believe that our current study, although preliminary, opens a new area of research. We are aware that we cannot suggest that serum testosterone levels decrease sodium excretion or increase sodium reabsorption along different nephron segments based on the results of the current study. Currently, we can only suggest that serum TT levels are independently associated with 24-hour urinary sodium excretion. Whether this relationship is due to decreased sodium excretion or increased sodium reabsorption requires further research.

We found that creatinine clearance and systolic BP were independently related to 24-hour urinary sodium excretion. These are not novel or unexpected findings. We found that increased age was related to decreased 24-hour sodium excretion. Urinary sodium reduction appears to increase with age, suggesting older individuals may generally be more health conscious and amenable to reducing their sodium use compared to younger individuals.[26-28] Decreased food intake with increasing age may also be responsible for the inverse association between age and 24-hour urinary sodium levels.

The exact mechanisms underlying the positive relationship between serum potassium and 24-hour urinary sodium levels are unknown. However, the relationship may be explained by the effects of aldosterone; unfortunately, in the current study, we did not evaluate aldosterone levels. Further studies are needed to examine whether the protective role of potassium against the development of hypertension is related to increased sodium excretion.

We did not find any association between age and testosterone levels in our study, which was unexpected. While the exact cause is unknown, the lack of association might be related to the relatively low patient age and the specific group of patients involved in the current study.

We are aware that our study has limitations that deserve mention. Firstly, since our study was cross-sectional, a cause and effect relationship cannot be suggested. Secondly, daily variability can be observed in the urinary sodium excretions of individuals, and urine samples were collected only once, which can be perceived as a relative limitation.[29] Additionally, sodium is a particular problem for dietary assessment because of the discretionary salt added in cooking and at the table which is not adequately captured by dietary instruments. The difficulties in assessing sodium intake with dietary instruments, coupled with large intra-individual variation, have led to recommendations that multiple, timed urine collections be used to characterize an individual's intake.[30] We did not evaluate the RAS system in our study. Our study sample was also relatively small, and we did not perform power analysis to calculate sample size. Still, as our study group was composed of newly-diagnosed stage 1 essential hypertensive patients who had no known history of cardiovascular diseases and were not currently on any antihypertensive medication, such as diuretics, the effects of cardiovascular co-morbidity and medication were potentially ruled out. Our findings cannot be generalized to other hypertensive patients, such as patients taking medication or stage 2 hypertensive patients. We are also aware that, although linear regression analysis showed an independent relationship between sodium excretion and age, creatinine clearance, systolic BP, potassium, and

testosterone, the correlations were relatively weak. Thus, we believe that our findings should be repeated in other patients.

In conclusion, we demonstrated that serum TT levels were independently related to 24-hour urinary sodium excretion. Whether testosterone increases sodium reabsorption or decreases sodium excretion along different nephron segments needs to be determined in essential hypertensive patients.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Blood pressure; body mass index; hypertension; hypertensive patients; renal function; sodium chloride/adverse effects; sodium/urine; total testosterone.

Anahtar sözcükler: Kan basıncı; beden kütle indeksi; hipertansiyon; hipertansif hastalar; böbrek işlevi; sodyum klorid/yan etkiler; sodyum/idrar; total testosteron.