Baseline Demographic, Clinical and Laboratory Parameters Related with 24 Hour Urinary Sodium Excretion in Newly Diagnosed Patients with Type 2 Diabetes

Yeni Tanı Almış Tip 2 Diyabetik Hastalarda 24 Saatlik İdrarda Sodyum Atılımı ile İlişkili Olan Demografik, Klinik ve Laboratuvar Parametrelerin Değerlendirilmesi

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ABSTRACT

OBJECTIVE: Hypertension is very frequently observed in patients with Type 2 diabetes. Increased salt intake has been shown to be related with elevated blood pressure. However, factors related with 24 hour urinary sodium (Na) excretion as a measure of Na intake is not specifically addressed in patients with newly diagnosed Type 2 diabetic patients.

MATERIAL and METHODS: All patients underwent history taking, physical examination, blood pressure measurement, electocardiography, biochemical analysis, spot urine analysis, 24-hour urine collection to measure 24-hour urinary albumin, protein, sodium excretion and creatinine clearance.

RESULTS: In total, 114 patients were enrolled. Spearman correlation analysis revealed that 24-hour urinary Na excretion was correlated with body mass index (BMI) (rho: 0.265, p: 0.004). blood urea nitrogen (rho: -0.210, p: 0.025) creatinine clearance (rho: 0.313, p: 0.001), albumin (rho: 0.320, p: 0.001), hemoglobin (rho: 0.242, p: 0.013) and triglyceride (rho: 0.261, p: 0.008). Linear regression of independent factors revealed that BMI (B: 0.013, CI: 0.004-0.022, P: 0.004), presence of smoking (B: 0.132, CI: 0.02-0.243, P: 0.021), creatinine clearance (B: 0.002, CI: 0.001-0.004, P: 0.012), and triglyceride levels (B: 0.017, CI: 0.009-0.056, P: 0.003) were related with logarithmically converted 24-hour Na excretion.

CONCLUSION: We demonstrated that BMI, creatinine clearance and serum triglyceride levels were independently associated with 24-hour urinary Na excretion in newly diagnosed Type 2 diabetic patients.

KEY WORDS: Creatinine, Type 2 diabetes, Hypertension

ÖZ

AMAÇ: Hipertansiyon Tip 2 diyabetli hastalarda sıklıkla görülen bir komplikasyondur. Bu hastalarda artmış tuz alımı hipertansiyon ile ilişkili bulunmuştur. Bununla birlikte literatürde tuz alımının bir göstergesi olarak 24 saatlik idrarda sodyum atılımını özellikle araştıran çalışmalar sınırlıdır. Biz bu çalışmamızda, yeni tanı almış tip 2 diyabetik hastalarda 24 saatlik idrarda sodyum atılımını etkileyen faktörleri araştırmayı amaçladık

GEREÇ ve YÖNTEMLER: Bütün hastaların tıbbı hikâyeleri alındı, fizik muayeneleri yapıldı, kan basınçları ölçüldü, elektrokardiografileri çekildi, biyokimyasal analizleri yapıldı, rutin idrar analizleri yapıldı ve 24 saatlik idrarda albümin, protein, sodyum atlımı ve kreatinin klirensi hesaplandı.

BULGULAR: Çalışmaya toplam 114 hasta dahil edildi. Spearman korelasyon analizinde 24 saatlik idrar sodyum atılımının vücut kitle indeksi (VKİ) ile (rho: 0,265, p: 0,004), kan üre nitrojeni ile (rho: -0,210, p: 0,025), kreatinin klirensi ile (rho: 0,313, p: 0,001), albümin ile (rho: 0,320, p: 0,001, hemoglobin ile (rho: 0,242, p: 0,013) ve trigliserid düzeyleri ile (rho: 0,261, p: 0,008) korrele olduğu görüldü. Doğrusal regresyon analizinde VKİ (B: 0,013, CI: 0.004-0,022, P: 0,004), sigara içme durumu

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(B: 0,132, CI: 0,02-0,243, P: 0,021), kreatinin klirensi (B: 0,002, CI: 0,001-0,004, P: 0,012)ve trigliserid düzeylerinin (B: 0,017, CI: 0,009-0,056, P: 0,003), 24 saatlik idrar sodyum atılımının bağımsız öngörücüleri olduğu bulundu.

SONUÇ: Çalışmamızda yeni tanı almış Tip 2 diyabetik hastalarda VKİ, kreatinin klirensi ve trigliserid düzeylerinin 24 saatlik idrar sodyum atılımı ile bağımsız olarak ilişkili oldugu saptandı.

ANAHTAR SÖZCÜKLER: Kreatinin, Tip 2 diyabet, Hipertansiyon

INTRODUCTION

It is well known that hypertension is extremely common in patients with type 2 diabetes (1). Although the full pathophysiologic mechanisms regarding elevated blood pressure in Type 2 diabetes is not completely understood; various mechanisms have been suggested. One of the most important factors is the effect of salt intake. In comparison to people without diabetes, patients with diabetes have an increase in exchangeable sodium (2,3). Blood pressure (BP) levels in patients with diabetes have been observed to be more salt-sensitive than in those without diabetes (4,5) and salt restriction augments the BP-lowering effects of antihypertensive medication in patients with type 2 diabetes (6,7). High sodium intake has also been shown to predict the development of type 2 diabetes. (8). Thus dietary salt intake may therefore have a more important role in the pathogenesis of hypertension in diabetes than in the general population. Surprisingly, although the importance of salt intake has been advocated in Type 2 diabetes, there are very scarce data present that examines the factors related with 24-hour urinary sodium (Na) excretion as a measure of Na intake in Type 2 diabetic patients.

In the current study, we evaluated the factors related with 24-hour urinary Na excretion in newly diagnosed type 2 diabetic patients who were hitherto treated by antihypertensives, oral glucose lowering agents and insulin.

METHODS

The current study was conducted in the outpatient nephrology unit of Konya Numune State Hospital between August 2010 and October 2011. The study was held in accordance with the declaration of Helsinki and local ethical approval and informed consent were obtained before enrolment. The study population consisted of patients with newly diagnosed type 2 diabetes who were hitherto treated. The diagnosis of type 2 diabetes mellitus was based on the arithmetic mean of 2 fasting plasma glucose levels (after at least 8 hours of fasting) using a cutoff point of 7.0 mmol/L, regardless of post-load plasma glucose concentrations (9). All patients underwent the following procedures: history taking, physical examination, BP measurement, electrocardiographic evaluation, biochemical analysis, spot urine analysis, 24-hour urine collection to measure 24-hour urinary albumin, protein, sodium excretion and creatinine clearance. The body mass index (BMI) was calculated as the ratio of weight in kilograms to height squared (in square meters). An information leaflet along with a urine container was given to all subjects and they also received a verbal explanation about how to collect a proper 24-hour urine sample. After excluding the first morning urine sample of the collection day, urine was collected over 24 h, which included the first urine sample of the next morning. During the sampling period, subjects were instructed to keep urine samples in a dark and cool place. At the end of the collection period, the urine containers were taken to the laboratory within 2–4 h. Since erroneous estimations of salt intake may occur according to problems in collecting 24-h urine samples, participants with urinary creatinine outside reference levels (reference intervals of 2.5%-97.5% for 24-hour urinary creatinine were accepted with 10.7 – 26.0 mg/kg/day for women and 12.1 – 28.9 g/kg for men) were excluded (10). Patients with coronary artery disease, heart failure, renal artery stenosis, rhythm problems, hypo or hypothyroidism, liver disease, urinary tract infection, urolithiasis, active infection and those who did not want to participate were excluded. None of the patients reported any alcohol intake.

Blood Pressure Measurement

A trained nurse measured blood pressure (BP). Seated clinic BP was measured manually with a mercury column sphygmomanometer and an appropriate size cuff after 5 minutes of rest according to AHA guidelines (11).

Laboratory Analysis

The laboratory parameters including 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), insulin, 24-hour urinary Na and protein levels were also measured.

Insulin resistance was calculated using the HOMA index, as follows: HOMA index = [fasting plasma glucose (in millimoles per liter) × fasting serum insulin (in microunits per milliliter)]/22.5(12). The levels of fasting glucose, urea, creatinine, and uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were determined by using

commercially available assay kits with an autoanalyzer (Architect ®c16000, Abbott Diagnostics, Abbott Park, Illinois, USA). Hemoglobin was measured by an automated blood analyzer (CELL-DYN 3700 cell counter Abbott Diagnostics Division, Abbott Laboratories, Illinois, USA). Serum sodium and potassium and urine sodium were measured by the direct potentiometric method by ion specific electrodes. 24-hour protein excretion was measured by the Benzethonium Chloride Method (Architect ®c16000, Abbott Diagnostics, Abbott Park, Illinois, USA). Albumin was measured by the bromcresol purple method. TSH, FT3, FT4 insulin levels were assayed by the direct chemiluminescence method (Advia Centaur XP, Siemens, Dublin, Ireland).

Statistics

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 and Spearman's correlation coefficient rho were used for correlations. For the comparison of 24-hour urinary Na excretion among normoalbuminuric, microalbuminuric and macroalbuminuric patients, the Kruskal-Wallis test was used. Stepwise linear regression analysis was performed to analyze the independent factors related with logarithmically converted 24-hour urinary sodium excretion. Variables tested for significance included gender, age, smoking status, body mass index, systolic BP, diastolic BP, albumin, hemoglobin, sodium, potassium, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, *glycated hemoglobin* (Hba1c), HOMA-index, 24 hour creatinine clearance and albumin excretion.

RESULTS

Initially 139 patients were enrolled. We excluded 1 patient with coronary artery disease, 1 patient with heart failure, 1 patient with renal artery stenosis, 1 patient with chronic liver disease, 2 patients with nephrotic syndrome, 2 patients with atrial fibrillation, 3 patients with hypothyroidism and 1 patient with hyperthyroidism, 2 patients with urinary tract infection, 5 patients who did not want to participate and 6 patients with incomplete 24-hour urine calculation from the study. The final patient population consisted of never treated 114 newly diagnosed patients with type 2 diabetes. The demographic and laboratory parameters of the patients are shown in Table I.

Table I: The demographic and laboratory parameters of 114 patients with Type 2 Diabetes.

Parameter*	
Age (years)*	45.2±10.2
Gender (Male/Female) (N:)	50/50
Body Mass Index (kg/m^2) *	30.1±5.4
Smoker/non smoker (N:)	22/92
Systolic Blood Pressure (mmHg) *	136.1±16.4
Diastolic Blood Pressure (mmHg) *	82.5±9.9
Serum glucose (mmol/L)*	9.29.±2.92
Blood urea Nitrogen (mmol/L)	9.85±5.89
Creatinine (μmol/L) *	129.1±64.5
Sodium (mmol/L) *	139.2±3.6
Potassium (mmol/L) *	4.73±0.62
Albumin (g/L) *	41.9±5.3
Hemoglobin (g/L) *	129.2±20.5
Basal Insulin Level (pmol/L) *	130.6±105.5
Total cholesterol (mmol/L) *	4.74±1.14
LDL-C (mmol/L) sı*	2.79±0.92
HDL-C (mmol/L) *	1.12±0.43
Triglyceride (mmol/L) *	2.04±1.06
Uric Acid (μmol/L) *	386.6±130.9
Thyroid Stimulating Hormone(mU/L) *	2.29±1.48
FT3(pg/ml) *	3.21±0.89
T4(ng/dl) *	1.22±0.32
Hba1c (%)*	7.14±1.65
24 hour urine albumin excretion rate (mg/day)*	321.8±492.7
24 hour urine protein excretion rate (mg/day)*	735.2±1124.1
24 hour urinary sodium excretion ((mEq/day)*	171.2±92.4
Creatinine clearance (ml/min)/1.73m^2*	68.6±38.3

*: Mean±Standard deviation. **LDL-C;** Low-density lipoprotein cholesterol, **HDL-C;** High-density lipoprotein cholesterol.

Correlations

Spearman correlation analysis revealed that 24-hour urinary Na excretion was correlated with BMI (rho: 0.265, p: 0.004), blood urea nitrogen (rho: -0.210, p: 0.025), creatinine clearance (rho: 0.313, p: 0.001), albumin (rho: 0.320, p: 0.001, hemoglobin (rho: 0.242, p: 0.013) and triglyceride (rho: 0.261, p: 0.008).

The 24-hour urinary Na excretion were 189.0±121.9, 165.3±88.8 and 169.5±73.9 mEq/day in normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively (P: 0.903). The scatter plot graphics of BMI, creatinine clearance and triglyceride with logarithmically converted 24-hour urinary sodium excretion are shown in Figures 1, 2 and 3 respectively.

Linear regression of independent factors (as mentioned above) has revealed that BMI, presence of smoking, creatinine clearance and triglyceride levels were related with logarithmically converted 24-hour Na excretion (as a dependent parameter) (Table II).

Table II: Linear regression of independent factors related with logarithmically converted 24-hour urinary sodium excretion.

	B	Beta	95% Confidence Interval	P
Body Mass Index	0.013	0.289	0.004-0.022	0.004
Presence of Smoking	0.132	0.225	0.02-0.243	0.021
Creatinine clearance	0.002	0.246	0.001-0.004	0.012
Triglyceride	0.017	0.288	0.009-0.056	0.003

B: Partial Regression Coefficient, **Beta:** Partial Correlation Coefficient.

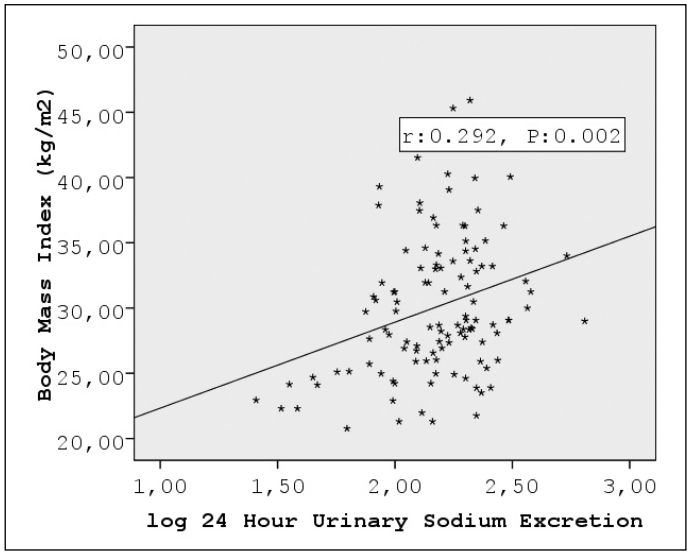

Figure 1: *The scatter plot graphic between body mass index and logarithmically converted 24-hour Urinary Sodium Excretion.*

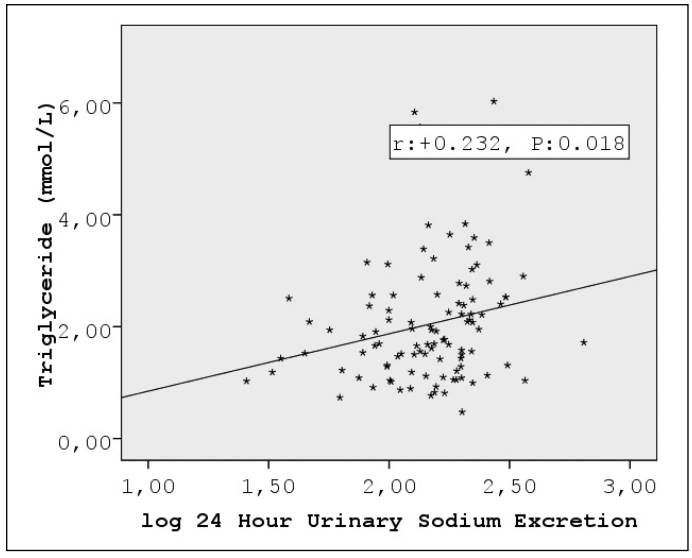

Figure 3: *The scatter plot graphic between triglyceride and logarithmically converted 24-hour Urinary Sodium Excretion.*

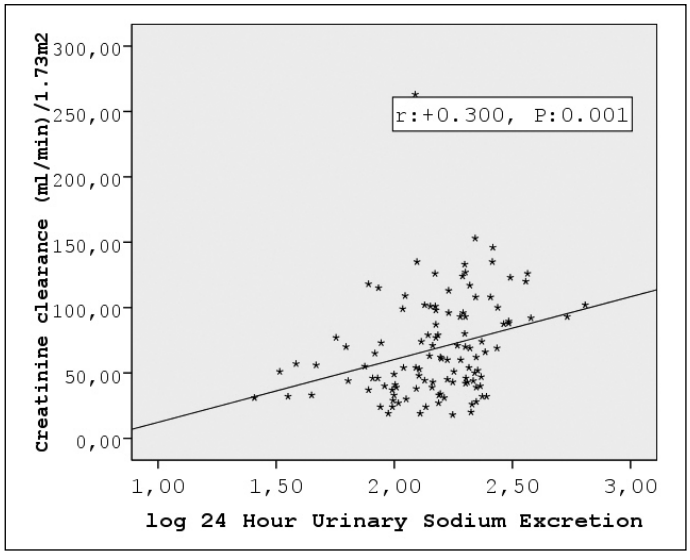

Figure 2: *The scatter plot graphic between creatinine clearance and logarithmically converted 24-hour Urinary Sodium Excretion.*

DISCUSSION

In the current study, to the best of our knowledge, we firstly examined the routine clinical and biochemical parameters related with 24-hour urinary Na excretion in newly diagnosed Type 2 diabetic patients who were hitherto treated. We demonstrated that BMI, smoking status, creatinine clearance and triglyceride levels were independently related with 24-hour urinary Na excretion.

It is known that patients with type 2 diabetes are frequently hypertensive. Numerous investigations have been carried out to determine the mechanism of hypertension in type 2 diabetes. Hyperinsulinemia and insulin resistance, increased vascular reactivity to various vasoconstrictors (13), activation of the the renin-angiotensin-aldosterone system (14), and increased sympathetic activity (15) were shown to be responsible factors for the presence of elevated BP in diabetic patients. However, studies have shown that the major mechanism regarding the cause of hypertension in type 2 diabetic patients was the effect

of salt intake. Previously it was shown that increases in total exchangeable sodium have been consistently found in diabetic patients (2,3,16,17). Secondly, increased sodium reabsorption along nephrons has been shown in diabetic patients (15,18-21). Thirdly, BP levels in patients with diabetes have been observed to be more salt-sensitive than in those without diabetes (4,5). Lastly salt restriction augments the blood pressure-lowering effects of antihypertensive medication in patients with type 2 diabetes (6,7). Thus all these data showed the importance of salt intake as a mechanism for increased BP in type 2 diabetic patients. Surprisingly however, very scarce data is present in the literature on the factors related with 24-hour urinary Na excretion as a measure of Na intake in type 2 diabetic patients.

As a novel finding we demonstrated that triglyceride levels were independently related with 24-hour urinary Na excretion. It is well known that overweight and obese people usually eat more food than normal weight people; along with a bigger quantity of food intake, they also get more sodium (8,22). Higher sodium intake may be associated with an unhealthy diet regarding other aspects of diet (8). Thus it is probable that patients eating high caloric diets get high fat along with high sodium as measured by the 24-hour urinary Na excretion. The relationship between BMI and Na excretion could also be explained in the context of increased high caloric diet. It could be hypothesized that more obese patients consume more salty foods. It could also be possible that since obese patients have higher creatinine clearance (23,24), and the relationship between BMI and Na excretion could be explained by the mechanism of increased GFR. However, the relationship between 24 hour urinary Na excretion and BMI is independent of creatinine clearance in the current study.

Of note in the current study is that we did not demonstrate any relationship between insulin resistance as evaluated by HOMA-Index and Na excretion. In the literature, the relationship between insulin resistance, 24-hour urinary Na excretion and salt sensitivity is conflicting. While some studies (25-28) have demonstrated that hyperinsulinaemia and insulin resistance were present in normotensive or hypertensive salt-sensitive patients; others did not show any relationship (29). The use of different methodologies to measure both salt sensitivity and insulin sensitivity may be the main reason explaining these conflicting results.

Lastly we found that the smoking habit is independently associated with 24-hour urinary Na excretion. Previously it was demonstrated that smokers have a less healthful diet than nonsmokers (30). In one metaanalysis it was demonstrated that smokers had significantly higher intakes of energy, total fat, saturated fat, dietary cholesterol, and alcohol, and significantly lower intakes of polyunsaturated fatty acids, fibre, vitamin C, vitamin E, beta carotene, iron, and calcium than nonsmokers (31). Apart from these differences it was also demonstrated that compared to never smokers, current smokers had higher 24-hour urinary Na excretion (32). Dietary Na intake in mg/day has also been found to be higher in smokers than nonsmokers in other studies (33,34). Thus by the light of our findings and previous findings we can suggest that smokers have less healthful diets including diets rich in fat, calories and sodium.

This study has several limitations that deserve mention. Firstly since the current study has a cross-sectional design, cause and effect relationship cannot be suggested. Secondly, analyses were based on single measurements and not on a serial basis. Thirdly, the study sample of the current study is relatively small. However, the study group was composed of special patients that included newly diagnosed type 2 diabetic patients who were not receiving any hypoglycemic and antihypertensive medication and the effects of medication were potentially ruled out.

In conclusion, we demonstrated that BMI, smoking habit, creatinine clearance and serum triglyceride levels were independently associated with 24-hour urinary Na excretion in newly diagnosed Type 2 diabetic patients. Further studies are needed to highlight underlying mechanisms regarding our findings.

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