The Relationship Between Daytime, Nighttime and 24-Hour Heart Rate with Urinary Albumin and Protein Excretion in Patients with Newly Diagnosed Type 2 Diabetes

Yeni Tanı Almış Tip 2 Diyabetli Hastalarda Gündüz, Gece ve 24 Saatlik Nabız Hızları ile İdrar Albumin ve Protein Atılımı Arasındaki İlişki

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ABSTRACT

OBJECTIVE: Autonomic nervous system dysfunction (ASD) has been widely observed in patients with type 2 diabetes. 24-hour ambulatory blood pressure (ABP) and heart rate measurements have been found to associate with ASD in patient with Type 2 diabetes. Since albumin excretion is also related with ASD in type 2 diabetes; in the current study, the relationships between daytime, nighttime and 24-hour heart rates with 24 hour urinary albumin excretion (UAE) and 24-hour urinary protein excretion (UPE) were analyzed in patients with newly diagnosed type 2 diabetes.

MATERIAL and METHODS: All patients underwent following procedures: history taking, physical examination, BP measurement, 12 lead electrocardiographic evaluations, routine urine analysis, biochemical analysis, 24-hour urine collection to measure UAE, UPE and creatinine clearance. 24-hour ABP and heart rate monitoring were performed for all patients.

RESULTS: In total 80 patients with newly diagnosed type 2 diabetes were included. Stepwise linear regression revealed that logarithmically converted 24-hour UAE were independently related with 24-hour ambulatory SBP, (P:0.001) and heart rate (night) (P<0.0001). Stepwise linear regression revealed that logarithmically converted 24-hour UPE were independently related with age (P:0.032), with averaged fasting blood glucose (P:0.023), with 24-hour ambulatory SBP, (P:0.002) and with heart rate (night) (P:0.001).

CONCLUSION: Nighttime heart rate, but not daytime and 24-hour heart rate was related with both 24-hour UAE and UPE in patients with Type 2 diabetes.

KEY WORDS: Ambulatory, Heart urinary albumin excretion, Urinary protein excretion, Type 2 diabetes

ÖZ

AMAÇ: Otonomik Sistem İşlev bozukluğu (OSİB) Tip 2 diyabetli hastalarda sık gözlenen bir durumdur. Tip 2 diyabeti olan hastalarda 24 saatlik ayaktan ölçülen nabız hızlarının OSİB ile ilişkili olduğu gösterilmiştir. Bununla birlikte bu hastalarda 24 saatlik idrarda protein atılımının (İPA) ve idrarda albümin atılımının (İAA) OSİB ile ilişkili olduğu bilinmektedir. Bütün bu bilgiler ışığında bu çalışmada yeni tanı almış tip 2 diyabeti olan hastalarda 24 saatlik İPA ve İAA ve gündüz, gece ve 24 saatlik nabız hızları ile olan ilişkisi araştırılmıştır.

GEREÇ ve YÖNTEMLER: Bütün hastaların tıbbı öyküleri alındı, fizik muayeneleri yapıldı, kan basınçları ölçüldü, elektrokardiyografileri çekildi, biyokimyasal analizleri yapıldı, rutin idrar incelemeleri yapıldı ve 24 saatlik İAA ve İPA ve kreatinin klirensi hesaplandı. Ayrıca bütün hastalara 24 saatlik kan basınçları (KB) ve nabız hızları ölçüldü.

BULGULAR: Çalışmaya toplam 80 yeni tanı almış tip 2 diyabetli hasta alındı. Basamaklı doğrusal regresyon analizinde 24 saatlik ayaktan sistolik KB (P:0,001) ve gece nabız hızı (P<0,0001) 24 saatlik İAA'nın bağımsız öngörücüleri olarak bulundu. Basamaklı doğrusal regresyon analizinde yaş (P:0,032), ortalama açlık kan şekeri (P:0,023), 24 saatlik ayaktan sistolik KB (P:0,002) ve gece nabız hızı (P:0,001) 24 saatlik İPA'nın bağımsız öngörücüleri olarak bulundu.

SONUÇ: 24 saatlik veya gündüz nabız hızları değil sadece gece nabız hızı idrarda 24 saatlik protein ve albümin atılımı ile ilişkili bulundu.

ANAHTAR SÖZCÜKLER: Nabız hızı, İdrar albumin atılımı, İdrar protein atılımı, Tip 2 diyabet

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INTRODUCTION

Autonomic dysfunction (AD) is very common in patients with type 2 diabetes (1-4). The association among microalbuminuria, cardiac autonomic neuropathy and diurnal blood pressure profile has been studied in type 2 diabetic subjects and the question of a causative relationship has arisen (1). Studies in type 2 diabetes have shown that abnormal diurnal variation in blood pressure (BP) is associated with microalbuminuria and autonomic neuropathy (5, 6). Previous studies have shown the urinary albumin excretion rate has been related to subclinical autonomic neuropathy in type 2 diabetic subjects (7,8). Another study demonstrated that the presence of autonomic neuropathy was associated with hyperinsulinemia and hypertriglyceridemia (9). Since heart rate is closely related with the balance of sympathetic and parasympathetic system (10), in the current study the relationship between autonomic dysfunction (as evaluated by 24-hour ambulatory heart rates), with 24 hour UPE and UAE were investigated in patients with newly diagnosed Type 2 diabetes.

METHODS

The study population of the current study consisted of patients with newly diagnosed type 2 diabetes who were hitherto treated. Diagnosis of type 2 diabetes mellitus was based on the American Diabetes Association criteria using at least 2 fasting plasma glucose levels (after at least 8 hours of fasting) regardless of post-load plasma glucose concentrations using a cutoff point of 7.0 mmol/L (11). The study was in accordance with the declaration of Helsinki and local ethical approval and informed consent was obtained before enrollment. All patients underwent the following procedures: history taking, physical examination, BP measurements, electrocardiographic evaluation, biochemical analysis, spot urine analysis, 24-hour urine collection to measure 24-hour UPE and UAE and creatinine clearance. During history taking demographic variables (age, sex), personality traits (smoking, alcohol intake, and clinical and laboratory parameters were recorded. Levels of averaged fasting blood glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, phosphorus, albumin, total cholesterol, high density lipoprotein cholesterol (HDL-Cholesterol), low density lipoprotein cholesterol (LDL-Cholesterol), and hemoglobin were measured. Patients with coronary artery disease, heart failure, cerebrovascular disease, essential hypertension, renal artery stenosis, rhythm problems, hypo or hypothyroidism, nephrotic syndrome, urinary tract infection, urolithiasis, with active infection and who did not want to participate were excluded. None of the patients reported any alcohol intake. 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 out of reference levels (reference intervals for 24-hour urinary creatinine were accepted as 10.7-26.0 g/kg for women and 12.1-28.9 g/kg for men) were excluded (12).

Ambulatory Blood Pressure Measurement

Ambulatory 24-hour BP monitoring was performed on each patient's nondominant arm using a SpaceLabs (Redmond, Washington, USA) 90207 oscillometric monitor. The accuracy of the device was checked against the standard auscultatory method to ensure that the difference in BP measurements between methods did not exceed +5 mmHg. The device was set to obtain BP readings at 20-minute intervals during the day (07:00 AM-11:00 PM) and at 30-minute intervals during the night (11:00 PM-07:00 AM). Each ambulatory BP monitoring dataset was first automatically scanned to remove artifactual readings according to preselected editing criteria. Data were edited by omitting all readings of zero, all heart rate readings <20 or >200, diastolic BP readings >150 and <40 mmHg, systolic BP readings >240 and <70 mmHg and all readings where the difference between systolic and diastolic BPs was less than 10 mmHg. Readings were evaluated if the percentage of successful readings were above 90%. The following ambulatory BP monitoring parameters were evaluated: Average ambulatory daytime systolic and diastolic BP levels (awake period), average ambulatory nighttime systolic and diastolic BP levels (asleep period), average ambulatory 24-hour systolic and diastolic BP levels, and mean ambulatory daytime, nighttime and 24-hour arterial BPs. Average ambulatory daytime, nighttime and 24-hour heart rates were also determined. All subjects were instructed to rest or sleep between 11:00 PM and 7:00 AM (nighttime) and to continue their usual activities between 7:00 AM and 11:00 PM (daytime). Patients were asked to remain still at the time of measurement and to note in a diary the occurrence of unusual events or poor sleep. "Nocturnal dipping" was defined as a reduction of > 10% (when compared with the daytime values) in the systolic and/or diastolic BP levels at night

Statistics

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Evanston, Illinois, USA). Results were considered statistically significant if two-tailed P value was less than 0.05. Data was checked for normality. Data are shown as means ± SD, unless otherwise noted. For the comparison of 24 hour UPE, UAE, and creatinine clearance among dipper and non-dipper patients Mann-Whitney U test was used. For the comparison of categorical variables Fisher's exact test was used. For correlation analysis Spearman correlation coefficient rho was used for non-normally distributed variables. Stepwise linear

regression analysis was performed to analyze the independent factors related with logarithmically converted 24-hour UPE and 24-hour UAE respectively (as dependent variables).

RESULTS

Initially 108 patients were included. 1 patient with coronary artery disease, 1 patient with heart failure, 1 patients with cerebrovascular disease, 3 patients with known hypertension, 1 patient with renal artery stenosis, 2 patients with atrial fibrillation, 2 patients with hypothyroidism, 1 patient with hyperthyroidism, 1 patients with nephrotic syndrome, 3 patients with urinary tract infection, 2 patients with urolithiasis, 1 patients with pneumonia, 3 patients who did not want to participate, and 6 patients with improper urine collection were excluded. The study was conducted in the remaining 80 patients with newly diagnosed type 2 diabetes. The demographic and laboratory characteristics of the patients were shown in Table I. The Ambulatory Blood Pressure and Heart Rate Measurements of the 80 Patients were shown in Table II.

Table I: The demographic and laboratory parameters of 80 patients with newly Diagnosed Type 2 Diabetes.

Parameter*		
Age (years)		50.4±9.2
Gender (Male/Female) (N:)		34/46
Body Mass Index (kg/m^2)		28.5±4.3
Smoker/non smoker (N:)		37/47
Systolic Blood Pressure (mmHg)		137.8±18.9
Diastolic Blood Pressure (mmHg)		78.6±12.0
Serum glucose (mmol/L) (range:4.2-6.4)		8.22±0.68
Hemoglobin (g/L)		138.2±14.6
BUN (mmol/L) (range:3.6-7.1)		6.42±2.24
Creatinine (μmol/L) (range:44.2-106.1)		89.2±52.1
Sodium (mmol/L)		140.1±3.64
Potassium (mmol/L)		4.42±0.45
Albumin (g/L)		44.4±4.3
Total cholesterol (mmol/L)		5.25±1.22
LDL-C (mmol/L)		3.03±0.92
HDL-C (mmol/L)		1.33±0.29
Triglyceride (mmol/L)		1.74±0.74
Uric Acid (μmol/L) (range:150-480)		341.4±94.6
Calcium (mmol/L) (range:2.2-2.6)		2.31±0.35
Phosphorus (mmol/L) (range:1-1.4)		1.12±0.19
Thyroid Stimulating Hormone(mU/L)		2.94±0.97
24 hour urine albumin excretion rate (mg/day)		384.5±833.2
24 hour urine protein excretion rate (mg/day)		751.7±1365.1
Creatinine clearance (ml/min)/1.73m^2		82.3±31.6
Aspartate Amino Transferase (μkat/L) (range:0-0.58)		0.37±0.16
Alanin Amino Transferase (μkat/L) (range:0-0.58)		0.40±0.17

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

The correlation coefficients of 24 hour UPE and UAE with ambulatory BP measurements and clinical variables were shown in Table III.

Comparison of dipper (N:34) and non-dipper (N:46) patients with regard to 24-hour UPE, UAE and creatinine clearance revealed that non dipper patients had higher 24-hour UPE (898.6 mg/day vs.516.6mg/day), higher 24-hour UAE (478.5 mg/day vs.257.4mg/day),whereas lower 24-hour creatinine clearance (80.8 ml/min/1.73m^2 vs. 84.3 ml/min/1.73m^2). However, none of these differences reached statistical significance (P>0.05, data not shown). Another finding of the present study was that only 8 patients had unchanged or increased nighttime heart rate when compared to daytime hear rate. Among these 8 patients 7 had non-dipper profile and 1 had dipper profile (P:0.129, Fisher's exact test)

Stepwise linear regression of factors including age, gender, body mass index, smoking status, presence of coronary artery disease, dipping status, averaged fasting blood glucose, 24-hour creatinine clearance, 24-h ambulatory SBP, 24-h ambulatory DBP, heart rate (day), heart rate (night) and (24-hour) revealed that logarithmically converted 24-hour UAE were independently related with 24-hour ambulatory SBP. (Table IV). Using the same

Table II: The Ambulatory Blood Pressure and Heart Rate Measurements of the 80 Patients with Type 2 Diabetes.

Parameter*	
Average ambulatory SBP (mmHg) (day)	134.5± 17.6
Average ambulatory DBP (mmHg) (day)	75.5± 9.3
Heart rate (day) (beats/min)	74.6±11.6
Average ambulatory SBP (mmHg) (night)	124.8±17.5
Average ambulatory DBP (mmHg) (night)	68.3±9.6
Heart rate (night). (beats/min)	63.8±9.9
Ambulatory SBP (mmHg) (24-h average)	132.7±17.3
Ambulatory DBP (mmHg) (24-h average)	73.8±8.7
Heart rate (24-h average) (beats/min)	71.4±9.5
Mean arterial BP (mmHg) (day)	95.3±11.2
Mean arterial BP (mmHg) (night)	87.3±11.0
Mean arterial BP (mmHg) (24-hour)	93.3±10.6

*: Mean ±Standard deviation.

Table III: The correlation coefficients of 24-hour UPE and UAE with ambulatory BP measurements and clinical variables.

Spearman's Correlation coefficient (rho) for	24-Hour UPE (rho)	P	24-Hour UAE (rho)	P
24-h ambulatory SBP	0.343	0.005	0.420	<0.0001
24-h heart rate	0.461	<0.0001	0.361	0.001
Ambulatory SBP (day)	0.345	0.005	0.436	<0.0001
Ambulatory DBP (day)	0.249	0.045	0.158	1.161
Heart rate (day)	0.372	0.002	0.306	0.006
Ambulatory SBP (night)	0.247	0.048	0.264	0.018
Heart rate (night)	0.538	0.0001	0.525	< 0.0001
Mean arterial BP (day)	0.380	0.002	0.330	0.005
Mean arterial BP (night)	0.278	0.026	0.200	0.094
Mean arterial BP (24-hour)	0.360	0.003	0.291	0.014
Averaged fasting blood glucose	0.309,	0.012	0.255	0.023
Hdl-cholesterol	-0.277,	0.026	-0.186	0.099
Serum Triglyceride	0.317	0.004	0.251	0.025

BP: Blood Pressure, **Hdl:** High Density Lipoprotein

Table IV: The multiple linear analyses of factors independently associated with 24-hour UAE and 24-hour UPE**.**

Parameter	B	95% CI	P
24-hour UAE			
24-hour ambulatory SBP	0.029	0.017-0.41	0.01
Heart rate (night)	0.05	0.03-0.069	<0.0001
24-hour UPE			
Age	-0.014	-0.027-(-0.001)	0.032
Fasting Blood Glucose	0.011	0.002-0.021	0.023
24-hour ambulatory SBP	0.013	0.005-0.020	0.002
Heart rate (night)	0.021	0.009-0.033	0.001

independent variables logarithmically converted 24-hour UPE were independently related with age with averaged fasting blood glucose, 24-hour ambulatory SBP, heart rate (night) (Table IV).

Of note, the Hba1c was available for 62 patients. The mean Hba1c was 7.46±1.26. Subgroup analysis revealed that Hba1c was correlated with 24-hour UPE (rho: 0.285, P:0.045) and 24-hour UAE (rho:0.318, P:0.012). Stepwise linear regression of above mentioned factors plus Hba1c were therefore carried out to find the independent relationship with these parameters and logarithmically converted 24-hour UAE and 24-hour UPE.

The subgroup stepwise linear regression analysis revealed that 24-hour UAE was independently related with 24-hour ambulatory SBP, (b:0.029, CI:0.017-0.041,) and heart rate (night) (b:0.055, CI:0.034-0.076, P<0.0001), averaged fasting blood glucose (b:0.020, CI:0.003-0.038, P:0.021) and Hba1c (b:0.250, CI:0.088-0.413, P:0.003). On the other hand 24-hour UPE was independently related with age (b:-0.026, CI:-0.038 (-)-0.013, P<:0.0001), with averaged fasting blood glucose (b:0.016, CI:0.007-0.024, P:0.001), 24-hour ambulatory SBP, (b:0.009, CI:0.002-0.016, P:0.014), heart rate (night) (b:0.024, CI:0.013-0.036, P:<0.0001) and Hba1c (b:0.148, CI:0.068-0.228, P:0.001)

DISCUSSION

In normotensive and hypertensive subjects, BP is characterized by a circadian pattern, with higher pressures during the day and lower pressures during the night (13). An important physiological mechanism behind this circadian BP pattern is the day-night variation in the activity of the autonomic nervous system (ANS), which, in turn, is under the influence of various intrinsic and extrinsic factors (14). The role of ANS in the generation of the circadian BP pattern is substantiated by conditions that affect the function of the ANS. For example, in patients neuropathy, the circadian variation of BP has been shown to be blunted or even reversed (15). Besides, it was shown that among diabetic patients, this phenomenon has been described to occur more often in individuals with autonomic neuropathy and with different degrees of diabetic nephropathy (16). The reasons why this abnormal pattern of BP is present more frequently in these groups of diabetic patients have not been completely elucidated. An increased extracellular volume (ECV) and nocturnal sympathetic predominance have been proposed as the mechanisms related to such BP abnormalities in patients with diabetic nephropathy and autonomic dysfunction (17). Previously heart rate variability as a measure of autonomic neuropathy has been found to be associated with urinary albumin excretion in Type 1 diabetic patients. The authors concluded that there is increased sympathetic activity during especially in

nighttime period and related to UAE and nocturnal non-dipping. In the current study it was also demonstrated that UAE and UPE were related with nighttime heart rate. However this study is different from that study in various aspects. Firstly this study was conducted in patients with type 2 diabetes and not on type 1 diabetic patients. Secondly the current study was conducted on patients with newly diagnosed patients who were hitherto treated. Thus we conclude that as in type 1 diabetes, patients with type 2 diabetes may have also impaired autonomic dysfunction and related sympathetic activation especially during night. We do not know why this abnormal pattern of blood pressure and heart rate were present in patients with type 2 diabetes but speculations could be made.

It was concluded that increased levels of plasma noradrenaline during sleep in type 2 diabetic patients with a minor BP decrease during the night. Additionally the increase in sympathetic activity observed by those authors was probably related to established autonomic neuropathy because the study included patients with longer diabetes duration and abnormal cardiovascular tests (17). Unfortunately, we did not measure adrenaline and noradrenaline levels in the current study. The sSecond mechanism was the increase of ECV. In one study it was demonstrated that the glomerular filtration rate (GFR) and ECV were significantly associated with the blunted nocturnal decline in BP in normoalbuminuric type 1 diabetic patients (18) . In another study it was shown that in the univariate analysis, the GFR and ECV were significantly associated with the blunted nocturnal decline in BP in normoalbuminuric type 1 diabetic patients; however this relation was lost in the multivariate analysis when the heart rate variability and urinary albumin excretion were included in the model. The authors concluded that sympathetic activity and urinary albumin excretion levels, even within the normal range, are stronger predictors of the blunted decline in nocturnal blood pressure in these patients (16). In the current study there was no correlation between GFR as evaluated with creatinine clearance with UAE, UPE. There were also no correlations between GFR, heart rate (day), heart rate (night) and heart rate (24-hour). ECV evaluation was not performed. Mmore studies are needed to show whether increased ECV is responsible for the activation of the sympathetic system during night. It is interesting to note that looking at the creatinine, creatinine clearance and albumin excretion levels, one may speculate that some of the patients have advanced disease although the patients were newly diagnosed as Type 2 diabetes. Twenty-five patients had already decreased creatinine clearance of <60 (ml/min)/1.73m^2 and 22 patients had a 24-hour UAE rate > 300 (mg/day) (data not shown). However, this is not a major limitation and indeed most of the patients are not aware of having diabetes. These patients probably had diabetes for a long time but were not aware of it. The results presented here therefore fit with everyday clinical practice and are valuable.This study has limitations that deserve mention. First, the design of the present study does not allow to assert whether a causal relationship exists regarding current findings. The activation of the sympathetic system was not evaluated specifically. The sample size was relatively small, suggesting the need for cautious interpretation of these findings. Still, we believe that the effects of cardiovascular comorbidity and medication were potentially ruled out since the study group was composed of special patients that included newly diagnosed type 2 diabetic patients without previous known cardiovascular diseases and who were not receiving any antihypertensive and oral hypoglycemic drugs.

In conclusion, nighttime heart rate but not daytime and 24-hour heart rate was related with both 24-hour UAE and UPE in patients with Type 2 diabetes. To the best of our knowledge there was no study in the literature which specifically addressed the relationship between daytime, nighttime and 24-hour heart rates and proteinuria. Studies are needed to analyze the nocturnal autonomic dysfunction in patients with type 2 diabetes.

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