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Research Article

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High-sensitivity C-reactive protein is associated with 24-hour ambulatory blood pressure variability in type 2 diabetes and control subjects

Proteina C-reactivă înalt sensibilă se asociază cu variabilitatea tensiunii arteriale monitorizată 24 ore ambulatoriu la subiecții cu diabet zaharat de tip 2 și control

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Abstract

Background and Aim: *Type 2 diabetes (T2DM) has been associated with hypertension (HTN) and elevated high-sensitivity C-reactive protein (hsCRP), but the possible implication of blood pressure (BP) variability in increasing hsCRP in T2DM are incompletely understood. We aimed to assess the association between hsCRP and BP variability during 24-hour ambulatory BP monitoring in T2DM and healthy control subjects.*

Material and Method: *The cross-sectional study included data from T2DM patients with normal BP (n=9), controlled HTN (n=46), uncontrolled HTN (n=20), and healthy controls (n=11). HsCRP was assessed using ELISA technique. All subjects underwent 24-hour ambulatory BP monitoring; BP variability was calculated using standard deviation.*

Results: *We found that hsCRP was associated with daytime and 24-hours systolic and diastolic BP variability. Higher hsCRP were observed in T2DM patients with uncontrolled HTN and high BP variability compared to the other three groups. In multiple regression analysis, hsCRP was predicted by daytime and 24-hour diastolic BP variability.*

Conclusions: *Our findings suggest that high hsCRP was associated with increased ambulatory BP variability in T2DM and control subjects. The contribution of both hsCRP and BP variability to cardiovascular risk stratification in T2DM needs to be evaluated in prospective studies.*

Keywords*: high-sensitivity C-reactive protein;diabetes mellitus;blood pressure variability;24-hour ambulatory blood pressure monitoring.*

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Rezumat

Premise şi scopul studiului: *Diabetul zaharat de tip 2 a fost asociat cu hipertensiunea arterială şi creşterea proteinei C-reactivă înalt sensibilă (hsCRP), însă posibila influenţă a variabilităţii tensiunii arteriale asupra hsCRP în diabetul zaharat de tip 2 este insuficient cunoscută. Ne-am propus să evaluăm asocierea dintre hsCRP şi variabilitatea tensiunii arteriale monitorizată ambulatoriu pe durata a 24 de ore la pacienţii cu diabet zaharat şi subiecţii control sănătoşi.*

Material şi Metodă: *Studiul transversal a inclus pacienţi cu diabet zaharat şi tensiune arterială normală (n=9), tensiune arterială controlată (n=46), tensiune arterială necontrolată (n=20), respectiv subiecţi control sănătoşi (n=11). HsCRP a fost măsurată folosind tehnica ELISA. Tensiunea arterială a fost monitorizată ambulatoriu timp de 24 de ore; variabilitatea tensiunii arteriale a fost evaluată folosind deviaţia standard.*

Rezultate: *HsCRP s-a asociat cu variabilitatea tensiunilor arteriale sistolică, respectiv diastolică din timpul zilei şi pe 24 de ore. Cele mai crescute valori ale hsCRP au fost observate în grupul pacienţilor cu diabet zaharat, tensiune arterială necontrolată şi variabilitate crescută a tensiunii arteriale. În regresie multiplă, hsCRP a fost prezisă de variabilitatea tensiunii arteriale diastolice din timpul zilei şi pe 24 de ore.*

Concluzii: *Valorile crescute ale hsCRP s-au asociat cu variabilitatea crescută a tensiunii arteriale la subiecţii cu diabetul zaharat de tip 2 şi control sănătoşi. Contribuţia concomitentă a hsCRP şi a variabilităţii tensiunii arteriale la statificarea riscului cardiovascular al pacienţilor cu diabet zaharat tip 2 trebuie evaluată în studii prospective.*

Cuvinte cheie*: proteină C-reactivă înalt sensibilă;diabet zaharat;variabilitate tensiune arterială;monitorizare ambulatorie pe 24 ore a tensiunii arteriale.*

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Introduction

The role of C-reactive protein (CRP) has been extensively investigated in relationship with the risk of cardiovascular events in studies including hypertensive patients, given the association of CRP with arterial stiffness and end-organ damage (1-4). The pathogenic mechanisms that contribute to type 2 diabetes mellitus (T2DM) development and progression also imply low-grade system inflammation (5). The presence of T2DM adds incremental value to the combination hypertension (HTN) and elevated high-sensitivity C-reactive protein (hsCRP) in associating multi-vessel coronary artery disease and in predicting coronary artery spasm, suggesting that these parameters should be incorporated into diagnostic strategies aimed to detect and manage cardiovascular disease (6,7). However, several studies reported that routine hsCRP measurement has low clinical outcome value for the cardiovascular disease risk estimation due to a lesser important association of CRP with cardiovascular events compared to other serum biomarkers (8-10).

On the other hand, high risk for organ damage and cardiovascular events were linked with increased blood pressure (BP) variability, regardless of the HTN severity (11,12). For this reason, the impact of BP variability needs to be considered just as much as BP control when evaluating hypertensive patients (13). Although variations in BP values are commonly noticed they are often underappreciated. BP variability can be estimated using the standard deviation (SD) of mean systolic and diastolic BP assessed using 24-hour ambulatory BP monitoring (24-hour ABPM) (14). It has been hypothesized that increased BP variability might be correlated with chronic systemic inflammation (15). A positive association between CRP and BP variability was found in normotensive, pre-hypertensive African Americans and hypertensive adults (16-19).

However, data reported on the relationship between BP variability and hsCRP in T2DM patients is very limited. Simultaneous measurement of these two parameters might offer a better understanding of the extent of BP variability impact on vascular inflammation. Therefore, we aimed to assess the association between hsCRP and BP variability during a 24-hour ambulatory BP monitoring in T2DM and healthy control subjects.

Materials and Methods

Patients

We performed a cross-sectional observational study involving 86 subjects. We enrolled consecutive Caucasian adult patients with T2DM (n=75) presenting to the Clinical Center of Diabetes, Nutrition and Metabolic Diseases in Cluj-Napoca, Romania, between July 2013 and February 2014. Patients were not included if they were previously diagnosed with unstable cardiovascular conditions, secondary hypertension, renal failure, inflammatory diseases or malignancies. T2DM patients (n=75) recruited in the study were divided into three groups: normal BP, controlled HTN and uncontrolled HTN according to a 24-hour ABPM. The control group consisting of heathy subjects without diabetes, hypertension or the previously listed exclusion criteria (n=11) was selected from the Internal Medicine Department, First Medical Clinic of the Emergency Clinical County Hospital in Cluj-Napoca, Romania.

In accordance with the World Medical Association Declaration of Helsinki revised in 2000, Edinburgh, and institutional guidelines, the protocol was approved by the local Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy in Cluj-Napoca, Romania. All participants were aware of the investigational nature of the study and provided written informed consent before any study procedure.

Study Protocol

Office systolic BP and diastolic BP were measured twice in both arms using an automatic device (Colin Press-Mate BP-8800C Sphygmomanometer Monitor, Japan) after 10 minutes of rest in a sitting position. The mean BP reading of the arm with the highest BP was used in the statistical analysis. Data related to personal medical history were collected accessing the patients' medical records, namely age, gender, T2DM duration, HTN duration and smoking status. T2DM was diagnosed according to the American Diabetes Association criteria (20). HTN was diagnosed according to the European Society of Hypertension criteria (21). Height, weight and abdominal circumference were recorded and body mass index was calculated.

Biochemical measurements

A blood sample was collected in the morning, before the medical examination and following overnight fasting. Glycated hemoglobin (HbA1c) was assessed immediately using commercially available methods (Hitachi, Roche Diagnostics). One blood sample from each subject underwent centrifugation and serum was stored until analysis at -80°C. HsCRP serum levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturers' instructions (DRG Instruments, GmbH, Marburg, Germany). The intra- and inter-assay coefficients of variation for hsCRP were about 5%.

Ambulatory blood pressure monitoring

After blood samples were obtained all subjects underwent a 24-h ABPM using a verified automatic device based on the oscillometric method, HolCARD CR-07 (Aspel, Poland), validated according to the Protocol of the European Hypertension Society. The arm with the highest blood pressure was used for 24-hour BP measurement. Readings were obtained every 30 min-

utes during daytime (7am-10pm) and every 60 minutes (10pm-7am) during nighttime. Subjects were instructed to engage in their normal activities during the 24-hour ABPM evaluation, but to refrain from strenuous physical activity and to keep their arm still and relaxed during measurements. All patients in this study had complete data on at least 70% of the total possible measurements. For each time period, we estimated the mean BP and the standard deviation (SD) of the BPs. The nocturnal systolic BP fall or dipping index (%) was calculated according to the formula: 100×(1– nighttime systolic BP/daytime systolic BP). According to the dipping index patients were classified as dippers if the nocturnal systolic BP fall was ≥10% and non-dippers if it was <10% (22). Controlled and normal BPs were defined as BP lower than 140/90mmHg (23). According to BP control and previous HTN diagnosis, T2DM patients were divided into three groups: normotensive or normal BP group (n=9), controlled HTN group (n=46) and uncontrolled HTN (n=20).

Statistical analysis

Data analysis was performed using the R 2.15.1 software for Windows. The Kolmogorov–Smirnov test was used to test the normal distribution of all variables. Data were expressed as mean ± standard deviation. The ANOVA was used to compare the groups' parametric variables. In post-hoc analysis for ANOVA, the Bonferroni procedure was used to compare the study groups. Relationships between variables were assessed using Pearson's or Spearman's correlation coefficients. A chi-square test was applied in order to verify the differences in frequency for nominal variables between the groups. Multiple linear regression analysis using the enter method was performed in order to predict the value of the dependent variable hsCRP based on values of the independent variables: abdominal circumference, body mass index, T2DM duration, age and HbA1c. In order to avoid collinearity, only one blood pressure parameter was introduced in the regression model at one time. A value of $p<0.05$ was considered statistically significant.

Results

Characteristics of the study population

The characteristics of the study participants are summarized in Table 1. We observed no significant differences in age, gender, smoking status and HbA1c between the four groups. We found significant differences in T2DM duration, HTN duration, body mass index, abdominal circumference, office systolic BP, office diastolic BP and hsCRP between the four groups. The highest hsCRP level was detected in the uncontrolled HTN T2DM group and was significantly higher than in the healthy control group (p=0.009).

Twenty Four-Hour Ambulatory Blood Pressure Monitoring

When analyzing 24-hour ABPM parameters we found significant differences in daytime, nighttime and 24-hour mean systolic BP and diastolic BP between the four groups (Table 2). Also, we observed significant differences in daytime and 24-hour systolic BP and daytime diastolic BP variability between the four groups. The highest systolic BP and diastolic BP variability was found in the uncontrolled HTN T2DM group. Daytime systolic BP and diastolic BP variability were significantly higher in the uncontrolled HTN T2DM group compared to the control group (p=0.027; p=0.031). Also, daytime and 24-hour systolic BP variability were significantly higher in the uncontrolled HTN T2DM group compared to the normal BP T2DM group (p=0.039; p=0.023). The control group had a higher normal dipper pattern frequency compared to normal BP, controlled HTN and uncontrolled HTN T2DM groups, but the difference did not reach statistical significance.

Table 1. Characteristics of the study population.

Variables	Healthy Controls *(n=11)*	Normal BP T2DM *(n=9)*	Controlled HTN T2DM *(n=46)*	Uncontrolled HTN T2DM *(n=20)*	p-value
Age (y)	54.1±8.0	57.4±7.6	60.5±6.5	58.3±8.7	NS
Sex M (%)	54.5	66.7	39.1	50	NS
Smoking status (%)	45.5	22.2	19.6	10	NS
T2DM duration(y)	0	5(0-11)	9.5(3-15)	6.5(0.8-10)	<0.001
HTN duration (y)	0	0	9(5-13)	6.5(4.2-14.6)	<0.001
BMI (kg/m2)	27.3±3.7	29.6±3.9	31.8±4.4	31.5±4.2	0.017
AC (cm)	100±9.8	107.0±11.5	110.2±10.0	110.4±10.2	0.030
Office SBP (mmHg)	118.2±8.4	127.5±16.9	133.8±14.8	145.6±12.6	<0.001
Office DBP (mmHg)	76.9±6.7	77.8±7.9	79.2±9.4	88.9±11.0	0.001
HbA1c (%)	<6.5	10.9±2.7	9.8±2.1	10.1±2.0	NS
hsCRP (mg/l)	0.48±0.15	0.56±0.11	0.68±0.32	0.84±0.43	0.015

T2DM, type 2 diabetes; BP, blood pressure; HTN, hypertension; BMI, body mass index; AC, abdominal circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein;
Values are means+/− standard deviation, median and interquartile range or percentages.

Table 2. The 24-hour ABPM parameters of controls, normal blood pressure type 2 diabetes, controlled hypertension type 2 diabetes and uncontrolled hypertensive type 2 diabetes patients.

Variables	Controls *(n=11)*	Normal BP T2DM *(n=9)*	Controlled HTN T2DM *(n=46)*	Uncontrolled HTN T2DM *(n=20)*	p-value
Day SBP (mmHg)	114.9±3.6	121.8±6.3	123.5±9.5	141.2±9.2	<0.001
Night SBP (mmHg)	103.1±7.1	117.1±9.7	114.7±12.3	131.0±10.9	<0.001
24-hour SBP (mmHg)	112.2±4.0	120.7±6.9	121.5±9.6	131.8±8.7	<0.001
Day SBP variability	7.4±2.3	7.2±3.1	9.7±3.2	10.8±4.5	0.017
Night SBP variability	7.2±1.5	8.4±2.9	9.0±3.3	10.2±4.6	NS
24-h SBP variability	9.2±1.7	8.0±2.7	10.6±3.4	12.0±4.7	0.028
Day DBP (mmHg)	76.0±4.1	77.0±6.8	75.5±8.1	89.4±7.7	<0.001
Night DBP (mmHg)	65.9±4.3	72.8±4.9	67.8±8.2	81.6±11.4	<0.001
24-hour DBP (mmHg)	73.7±3.6	76.0±6.0	73.7±7.8	87.5±8.1	<0.001
Day DBP variability	6.2±1.5	7.2±1.7	7.2±1.8	8.4±2.9	0.048
Night DBP variability	6.8±1.3	7.5±2.0	7.3±2.2	7.6±3.1	NS
24-h DBP variability	7.9±1.6	7.7±1.6	8.1±1.9	9.5±2.7	NS
Dipper Pattern (%)	46%	11%	32.6%	30%	NS

BP, blood pressure; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; Values are means+/− standard deviation or percentages.

Correlations

In the study population, we found that hsCRP was significantly and directly associated with daytime mean systolic BP, daytime and 24-hour systolic BP variability and daytime and 24-hour diastolic BP variability (Table 3). HsCRP levels were not associated with night-time or 24-hour mean systolic and diastolic BP (data not shown), abdominal circumference, body mass index, HbA1c, age, T2DM duration, and HTN duration.

Table 3. Correlations of hsCRP.

	hsCRP		
	r	95% CI	*p*-value
Day SBP	0.22	0.01 to 0.42	0.047
Day SBP variability	0.24	0.04 to 0.42	0.025
24-h SBP variability	0.24	0.05 to 0.41	0.026
Day DBP variability	0.23	0.01 to 0.47	0.033
24-h DBP variability	0.24	0.01 to 0.42	0.029
AC	0.02	-0.18 to 0.23	0.864
BMI	-0.4	-0.29 to 0.21	0.731
HbA1c	0.02	-0.18 to 0.20	0.882
Age	-0.13	-0.41 to -0.18	0.27
T2DM duration	-0.04	-0.23 to 0.17	0.749
HTN duration	-0.01	-0.20 to 0.19	0.957

hsCRP, high-sensitivity C-reactive protein;
SBP, systolic blood pressure; DBP, diastolic blood pressure; AC, abdominal circumference; BMI, body mass index; HbA1c, glycated hemoglobin; T2DM, type 2 diabetes; HTN, hypertension.

Multiple Linear Regression Analysis

When hsCRP was predicted using multiple linear regression analysis, we found that daytime and 24-hour diastolic BP variability were significant independent predictors in two separate models. The results were adjusted for abdominal circumference, body mass index, age, T2DM duration and HbA1c. The overall models fit were R^2=0.08 (model 1) and R^2=0.09 (model 2) (Table 4).

Discussion

The most important finding of the present study is that hsCRP was significantly associated with daytime and 24-hour systolic and diastolic BP variability. HsCRP levels were independently predicted by daytime and 24-hour diastolic BP variability, regardless of the adjustment for

Table 4. Multiple linear regression analysis using the enter method to predict the dependent variable hsCRP.

		Unstandardized coefficients		Standardized coefficients	P-value	95% Confidence interval for B	
		B	SE	Beta		Lower bound	Upper bound
Model 1	(Constant)	0.981	0.639		0.130	-0.295	2.257
	Day DBP variability	0.039	0.019	0.252	0.044	0.001	0.077
	AC	0.002	0.006	0.071	0.693	-0.010	0.015
	BMI	-0.008	0.014	-0.098	0.583	-0.036	0.020
	T2DM duration	-0.001	0.006	-0.002	0.988	-0.012	0.012
	Age	-0.008	0.006	-0.173	0.170	-0.21	0.004
	HbA1c	-0.007	0.021	-0.042	0.741	-0.048	0.034
Model 2	(Constant)	0.808	0.640		0.212	-0.471	2.086
	24-h DBP variability	0.043	0.019	0.273	0.027	0.005	0.081
	AC	0.002	0.006	0.071	0.690	-0.010	0.015
	BMI	-0.008	0.014	-0.102	0.565	-0.036	0.020
	T2DM duration	0.001	0.006	0.025	0.084	-0.011	0.013
	Age	-0.007	0.006	-0.148	0.226	-0.019	0.005
	HbA1c	-0.004	0.020	-0.025	0.841	-0.045	0.037

DBP, diastolic blood pressure; AC, abdominal circumference; BMI, body mass index; T2DM, type 2 diabetes; HbA1c, glycated hemoglobin.

behavioral and clinical confounders. Also, significantly higher hsCRP levels were found in T2DM patients with uncontrolled HTN and high BP variability compared to healthy control subjects. Together, these results suggest that hsCRP might be better associated to cardiovascular risk through BP variability than mean BP values in T2DM patients.

Although HTN has been established to be a predictor for cardiovascular disease, the concept of 24-hour systolic BP and diastolic BP variability might also have a prognostic impact. Even when trying to control the factors that might influence BP variability, such as patients' anxiety or accuracy of the measurement technique, it is known that BP has biological short-term (e.g. minute-to-minute) and long-term variations. All these BP variations had comparable effects on cardiovascular risk events (24). However, SD has been questioned as an appropriate estimator of BP variability, considering that it is sensitive to the number of BP measurements and it is calculated as dispersion values around the BP mean (25). Although other methods were described for measuring BP variability, we demonstrated that SD was a useful parameter to assess BP variability given the ability of 24-hour diastolic BP variability to independently predict hsCRP levels in T2DM patients (18). When analyzing BP variability using the SD of ambulatory BPs, we found similar results as previous studies did, indicating an average magnitude of 9 to 12 mmHg for the systolic BP and 6 to 9 mmHg for the diastolic BP (13). BP variability is increased in hypertensive compared to normotensive patients and increases with the severity of HTN (26,27). We found that the highest systolic BP and diastolic BP variability were detected in the uncontrolled HTN T2DM group.

Similar results regarding the association of BP variability with CRP were previously reported in hypertensive adults (18,19). In addition, our study offers new insights in the simultaneous measurement of hsCRP and BP variability in hypertensive T2DM patients. Abramson et al. suggested that low grade inflammation may be one of the factors that promote increased BP variability in normotensive middle-aged adults (16). According to our results, increased BP variability, particularly daytime and 24-hour diastolic BP variability were the factors that predicted the hsCRP levels.

Since the independent presence of T2DM, BP variability and hsCRP was previously demonstrated to have a predictive value for the development of cardiovascular disease, their additive effect might result in a more increased cardiovascular risk (19). The American Heart Association published a statement which recommended the use of hsCRP to evaluate the risk for heart disease in the adult population. The lowest cut-off points for hsCRP stratification risk were lower than 1mg/l for low risk and higher than 3mg/l for high risk (28). The contribution of hsCRP and ambulatory BP variability to cardiovascular risk stratification in T2DM and control subjects needs to be evaluated in prospective studies.

Analyzing the dipper pattern, we found that the normal BP T2DM had the lowest percentage of dipper pattern among the study groups, although all BP values were within normal range. A possible explanation for the higher prevalence of dipper pattern in the HTN groups compared to the normal BP group might relay in the beneficial effect of HTN treatment on nocturnal BP fall (29). The authors previously demonstrated that ingestion of at least one HTN medication at bedtime positively influenced the dipper pattern in T2DM and control subjects (30). A future evaluation is needed to assess the effect HTN and T2DM medication on nocturnal BP fall.

Conclusions

We demonstrated that hsCRP was associated with daytime and 24-hour systolic BP variability,

and daytime and 24-hour diastolic BP variability. Also, ambulatory BP variability assessed as daytime and 24-hour diastolic BP variability were independent predictors for hsCRP. The highest hsCRP levels were detected in T2DM patients with uncontrolled HTN and high BP variability.

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Conflicts of interest

None of the authors has any potential financial conflict of interest related to this manuscript

Abbreviations

24-hour ABPM - 24-hour Ambulatory Blood Pressure Monitoring
AC - abdominal circumference
BMI - body mass index
BP - blood pressure
DBP - diastolic blood pressure
HbA1c - glycated hemoglobin
HsCRP - high-sensitivity C-reactive protein
HTN - hypertension
SBP - systolic blood pressure
SD - standard deviation
T2DM - type 2 diabetes mellitus

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