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Intercellular adhesion molecule-1 (ICAM-1) associates with 24-hour ambulatory blood pressure variability in type 2 diabetes and controls

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ABSTRACT

Background and aim: Endothelial dysfunction is a common feature in hypertension and type 2 diabetes. Whether blood pressure (BP) variability is influencing serum intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) remains to be clarified. We aimed to assess the association between the circulating adhesion molecules and ambulatory blood pressure variability in patients with type 2 diabetes and controls.

Patients and methods: The study included data from type 2 diabetes with controlled BP (n = 55), type 2 diabetes with uncontrolled BP (n = 55) and control subjects (n = 28). ICAM-1 and VCAM-1 were measured with specific enzyme–linked immunosorbent assay method. BP variability was assessed using standard deviation of mean systolic and diastolic BP evaluated during 24-hour ambulatory BP monitoring.

Results: The uncontrolled BP type 2 diabetes group had significantly higher serum ICAM-1 and VCAM-1 levels compared to controlled BP type 2 diabetes and control groups. In linear regression analysis, after adjustment, higher ICAM-1 was consistently associated with higher daytime and 24-hour diastolic BP variability, and daytime systolic BP variability in the study population. VCAM-1 was associated only with daytime systolic BP variability.

Conclusions: Our study evaluating the association of serum ICAM-1 and VCAM-1 with 24-hour ambulatory BP variability in patients with type 2 diabetes and controls might offer better understanding of the mechanisms generating endothelial dysfunction. Elevated 24-hour ambulatory BP variability might induce endothelial activation by increasing circulating adhesion molecules levels.

1. Introduction

Hyperglycaemia [1,2] and high blood pressure (BP) [3,4] lead to systemic and vascular subclinical inflammatory status and induce endothelial damage. The inflammatory response involving endothelium activation and expression of circulating adhesion cells intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) was reported in the development of atherosclerotic lesions, cardiovascular disease [5–7] and chronic diabetes complications [8,9]. Patients with type 2 diabetes (T2DM) express higher levels of ICAM-1 [1,8] and VCAM-1 [11] compared to controls. Also, significantly higher circulating adhesion cells levels have been detected in patients with hypertension patients compared to their normotensive peers [3,11]. Diabetes and hypertension seem to have synergic effect on circulating adhesion cells levels, and their coexistence might have an additive effect [12–14].

The 24-hour ambulatory BP variability, calculated as standard deviation of mean systolic and diastolic BP [15], has been shown to be an independent cardiovascular risk factor as important as BP control when evaluating hypertension [16–18]. The influencing effect of ambulatory BP variability on chronic inflammatory markers has been previously described [19–21], but its relation with the circulating adhesion molecules remains to be clarified. The study of the association between BP variability and expression of circulating adhesion molecules is particularly important in patients with T2DM, who are at risk of presenting higher ambulatory BP variability compared to non-diabetic peers [22] and for whom the cardiovascular protection is more likely to be effectively achieved if tight BP control is implemented early [23]. In this

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context, we aimed to assess the relationship between circulating adhesion molecules, ICAM-1 and VCAM-1, and ambulatory BP variability in patients with T2DM and controls.

2. Methods

2.1. Study design and patients

This was a cross-sectional study performed in the Department of Diabetes and Nutrition, Emergency Clinical County Hospital in Cluj-Napoca, Romania. 110 consecutive patients previously diagnosed with T2DM according to the American Diabetes Association criteria [24] and 28 normoglycemic persons matched for age, sex and smoking status were enrolled between July 2013 and February 2014, and June-July 2018. The patients with T2DM were categorised into two groups: controlled BP (BP lower than 140/90; n = 55) and uncontrolled BP (n = 55) according to mean BP values during 24-hour ambulatory BP monitoring [25]. Patients were not included if they had: unstable cardiovascular conditions, secondary hypertension, renal or hepatic failure, inflammatory diseases, malignancies or were pregnant.

The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and institutional guidelines. The study protocol was approved by the local Ethics Committee of the Iuliu Haţieganu University of Medicine and Pharmacy in Cluj-Napoca, Romania. All participants provided written informed consent before any study procedure.

2.2. Study protocol

Data on age, sex, duration of diabetes, duration of hypertension, smoking status, medical history and current medication was collected during patients' interviews and from patients' medical files. Hypertension was diagnosed in the presence of office BP of ≥140 mmHg systolic or ≥90 mmHg diastolic or the use of antihypertensive drugs [26]. Height and weight were measured in fasting state, light dress and with no shoes, and body mass index was calculated. Systolic BP and diastolic BP were measured twice in both arms after 10 min of rest in a sitting position using an automatic device (Colin Press-Mate BP-8800C Sphygmomanometer Monitor, Japan). The mean of BP reading measured on the arm with the highest BP was recorded as office BP. Controlled and normal BP were defined as BP lower than 140/90 mmHg [26].

Fasting blood samples were obtained for the assessment of HbA1c, glycemia, ICAM-1 and VCAM-1. Serum levels of ICAM-1 and VCAM-1 were quantified using commercially available enzyme-linked immunosorbent assay kits according to the manufacturers' instructions (USCN, Life Science Inc., Wuhan, China) in the Laboratory of Immunology of the Emergency County Hospital Cluj, Romania. The kit detection range of ICAM-1 was between 0.078 and 5 ng/mL and of VCAM-1 was between 0.78 and 50 ng/mL. The serum levels of ICAM-1 and VCAM-1 were calculated using reference to standard curves concentrations performed for each corresponding molecule. The sensitivity of the ELISA system was less than 0.036 ng/mL for ICAM-1 and less than 0.32 ng/ml for VCAM-1. The inter-assay coefficient of variance was less than 12%, while the intra-assay coefficient of variance was less than 10% for both ICAM-1 and VCAM-1. The results reported in our study were obtained after preparing serum dilutions of 1/50 for both ICAM-1 and VCAM-1. Glycemia and HbA1c were assessed using commercially available methods (Hitachi, Roche Diagnostics).

2.3. 24-hour ambulatory blood pressure monitoring

After blood samples collection, all study participants were initiated on 24-hour ambulatory BP monitoring using a validated and calibrated automatic device (HolCARD CR-07; Aspel, Poland). The arm with the highest office BP was used for measuring BP every 30 min during daytime period (7am–10 pm) and every 60 min (10 pm–7am) during the nighttime period. Patients were instructed to carry out their usual activities, but to avoid intense physical activity and to keep their arm relaxed during BP measurements. All patients had complete data on at least 27 (70%) of the 39 possible measurements. We used standard deviation of mean BP as indices of short-term reading of BP variability. For each time period, we estimated mean systolic and diastolic BP and standard deviation of mean systolic and diastolic BP of all individual readings over the 24-hour as well as daytime and nighttime periods.

2.4. Statistical analysis

Descriptive statistics were expressed as number and percentages, mean ± standard deviation, median or percentile (25th and 75th) after assessing the normal distribution using Kolmogorov-Smirnov test. Correlations were performed to assess relations between ICAM-1, VCAM-1 and other variables using Spearman coefficient. Group comparisons of all variables were performed using ANOVA, Kruskall-Wallis and chi-square test. Linear regression analysis, adjusted for age, sex, body mass index, smoking status, presence of diabetes and fasting plasma glucose, was performed to predict the value of the dependent variables ICAM-1 and VCAM-1 based on the values of independent variables. ICAM-1 and VCAM-1 had a non-Gaussian distribution and therefore were logarithmically transformed before inclusion in the regression analysis. Prior to performing the linear regression analysis, collinearity diagnostic was performed for all BP variability parameters. As the variables included as predictors displayed variation inflation factors > 10, it was decided not to perform multiple regression analysis due to collinearity issues among predictors. Statistical analyses were performed using R 2.15.1 and LibreOffice programs. Statistical significance threshold was considered $p < 0.05$.

Table 1
The characteristics of the study groups.

Variables	Controls *(n = 28)*	Controlled BP T2DM *(n = 55)*	Uncontrolled BP T2DM *(n = 55)*	p-value
Age (years)	58.5 (46.5–68.5)	60.0 (57.0–64.0)	62.0 (54.5–67.0)	0.619
Male sex n, (%)	9 (32.1)	24 (43.6)	26 (47.3)	0.420
Smoking status n, (%)	6 (21.4)	11 (20.0)	3 (5.5)	0.066
Body mass index (kg/m^2)	28.1 ± 4.6	31.5 ± 4.5	33.9 ± 5.6	< **0.001**
Office systolic BP (mmHg)	126.8 ± 17.4	132.8 ± 15.2	149.6 ± 16.4	< **0.001**
Office diastolic BP (mmHg)	79.0 ± 10.7	79.0 ± 9.2	87.8 ± 12.8	< **0.001**
HbA1c (%)	< 5.7	9.9 ± 2.2	9.4 ± 2.1	< **0.001**
Fasting glycemia (mg/dl)	96.4 ± 9.5	173.3 ± 45.7	169.1 ± 49.5	< **0.001**
ICAM-1 (ng/ml)	484 (303–780)	506 (452–593)	860 (562–2780)	< **0.001**
VCAM-1 (ng/ml)	766 (699–881)	860 (715–1040)	987 (735–1363)	**0.009**

BP, blood pressure; T2DM, type 2 diabetes; HbA1c, glycated haemoglobin; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1. Values are means ± standard deviation, median and percentile (25th and 75th) or number and percentages.

3. Results

3.1. Characteristics of the study participants

The characteristics of the study population are presented in Table 1. We observed no significant differences in age, sex and smoking status between the three groups. As expected, body mass index, glycated haemoglobin (HbA1c), glycemia, office systolic and diastolic BP were significantly higher in the controlled and uncontrolled BP T2DM groups compared to the control group. ICAM-1 and VCAM-1 levels were higher in the uncontrolled BP T2DM group compared to the controlled BP T2DM and the control groups. Also, there were significant differences in ICAM-1 and VCAM-1 levels between the three groups. Diabetes duration, 9.1(3.0–13.0) vs. 8.0 (3.0–12.5) years (p = 0.75), and hypertension duration, 7.7(3.0–13.0) vs. 9.0(5.0–14.0) years (p = 0.38), did not differ between the controlled BP and uncontrolled BP T2DM groups. Patients from controlled and uncontrolled BP T2DM groups were receiving treatment with statins (76.4% vs. 89.1%), oral antidiabetic drugs (22.0% vs. 96.4%), insulin (78.9% vs. 78.2%) and antihypertensive drugs (85.5% vs. 92.7%).

3.2. 24-hour ambulatory blood pressure monitoring

The 24-hour ambulatory BP monitoring parameters of the three study groups are summarized in Table 2. We observed significantly higher daytime, nighttime and 24-hour mean systolic and diastolic BP in the uncontrolled BP T2DM group. Also, we found significant differences in daytime, nighttime and 24-hour diastolic BP variability, and, daytime and 24-hour systolic BP variability between the three study groups. Significantly higher nighttime systolic BP variability were observed in the uncontrolled BP T2DM group compared to controlled BP T2DM group ($p < 0.001$).

3.3. Correlations of circulating adhesion molecules

In the whole study population analysed irrespective of diabetes mellitus presence and BP control status, ICAM-1 was significantly and directly correlated with daytime and nighttime systolic BP variability, daytime and 24-hour diastolic BP variability, mean systolic BP during daytime, nighttime and 24-hour periods, office systolic and diastolic BP. No correlations of VCAM-1 with the assessed BP parameters were observed (Table 3). In the study population, VCAM-1 correlated with ICAM-1 ($r = 0.55$; $p < 0.001$).

When correlations were analysed only in patients with T2DM, we found similar results for ICAM-1. ICAM-1 was significantly and directly correlated with all previously mentioned BP parameters, except for nighttime systolic BP variability and office diastolic BP. In addition, we observed significant correlations of VCAM-1with daytime diastolic BP variability and ICAM-1 ($r = 0.55$; $p < 0.001$) (Table 4).

Table 3
The correlations of ICAM-1 and VCAM-1 with 24-hour ambulatory blood pressure parameters and office blood pressure in the whole study population.

	ICAM-1		VCAM-1	
	r*	p-value	r*	p-value
Daytime systolic BP variability	0.18	**0.034**	0.14	0.116
Night-time systolic BP variability	0.17	**0.049**	0.14	0.109
24-hour systolic BP variability	0.14	0.100	0.10	0.265
Daytime diastolic BP variability	0.33	< **0.001**	0.11	0.192
Nighttime diastolic BP variability	0.05	0.57	−0.05	0.569
24-hour diastolic BP variability	0.26	**0.002**	0.08	0.335
Daytime mean systolic BP	0.36	< **0.001**	0.13	0.130
Nighttime mean systolic BP	0.35	< **0.001**	0.16	0.060
24-hour mean systolic BP	0.37	< **0.001**	0.14	0.095
Daytime mean diastolic BP	0.10	0.244	0.06	0.460
Night-time mean diastolic BP	0.14	0.104	0.08	0.344
24-hour mean diastolic BP	0.11	0.203	0.06	0.458
Office systolic BP	0.23	**0.006**	0.10	0.252
Office diastolic BP	0.18	**0.039**	0.02	0.832

* Spearman coefficient; BP, blood pressure.

Table 4
The correlations of ICAM-1 and VCAM-1 with 24-hour ambulatory blood pressure parameters and office blood pressure in persons with T2DM.

	ICAM-1		VCAM-1	
	r*	p-value	r*	p-value
Daytime systolic BP variability	0.22	**0.023**	0.16	0.094
Nighttime systolic BP variability	0.16	0.104	0.105	0.274
24-hour systolic BP variability	0.17	0.079	0.09	0.329
Daytime diastolic BP variability	0.36	< **0.001**	0.20	**0.034**
Nighttime diastolic BP variability	0.08	0.416	0.14	0.137
24-hour diastolic BP variability	0.32	**0.001**	−0.09	0.377
Daytime mean systolic BP	0.37	< **0.001**	0.13	0.187
Nighttime mean systolic BP	0.39	< **0.001**	0.11	0.243
24-hour mean systolic BP	0.38	< **0.001**	0.10	0.295
Daytime mean diastolic BP	0.16	0.095	0.06	0.554
Nighttime mean diastolic BP	0.18	0.057	0.08	0.384
24-hour mean diastolic BP	0.163	0.089	0.06	0.558
Office systolic BP	0.23	**0.016**	0.06	0.506
Office diastolic BP	0.17	0.08	−0.02	0.865

* Spearman coefficient; BP, blood pressure.

3.4. Linear regression analysis for ICAM-1 and VCAM-1 prediction

In linear regression analysis, we found that ICAM-1 was significantly associated with daytime systolic BP variability, daytime and 24-hour diastolic BP variability, mean systolic BP during daytime, nighttime and 24-hour periods, nighttime mean diastolic BP and office systolic BP. VCAM-1 was associated only with daytime systolic BP

Table 2
The 24-hour ambulatory blood pressure parameters of the study groups.

Variables	Controls *(n = 28)*	Controlled BP T2DM *(n = 55)*	Uncontrolled BP T2DM *(n = 55)*	p-value
Daytime mean systolic BP	120.0 ± 9.5	123.3 ± 9.1	145.1 ± 12.5	< **0.001**
Nighttime mean systolic BP	111.9 ± 14.1	115.2 ± 11.9	136.9 ± 13.1	< **0.001**
24-hour mean systolic BP	118.1 ± 10.2	121.4 ± 9.3	143.2 ± 12.1	< **0.001**
Daytime systolic BP variability	8.8 ± 3.2	9.3 ± 3.3	10.9 ± 4.2	< **0.001**
Nighttime systolic BP variability	10.1 ± 5.0	8.9 ± 3.2	13.2 ± 6.6	**0.007**
24-hour systolic BP variability	10.7 ± 3.5	10.2 ± 3.5	13.0 ± 4.3	**0.001**
Daytime mean diastolic BP	74.1 ± 8.2	75.8 ± 7.9	86.3 ± 11.1	< **0.001**
Nighttime mean diastolic BP	67.3 ± 7.3	68.7 ± 8.0	77.7 ± 12.7	< **0.001**
24-hour mean diastolic BP	72.5 ± 7.6	74.0 ± 7.6	84.3 ± 11.1	< **0.001**
Daytime diastolic BP variability	8.3 ± 3.1	7.2 ± 1.8	10.3 ± 3.4	< **0.001**
Nighttime diastolic BP variability	8.5 ± 2.5	7.4 ± 2.2	8.6 ± 3.4	0.067
24-hour diastolic BP variability	9.2 ± 2.3	8.1 ± 1.9	11.0 ± 3.0	< **0.001**

BP, systolic blood pressure. Values are means ± standard deviation.

Table 5
The linear regression analysis for the dependent variables lgICAM-1 and lgVCAM-1 in the whole study population.

	lgICAM-1		lgVCAM-1	
	Beta standardized coefficients	*p*-value	Beta standardized coefficients	*p*-value
Daytime systolic BP variability	**0.295**	**0.005**	**0.225**	**0.036**
Nighttime systolic BP variability	0.096	0.337	0.114	0.257
24-hour systolic BP variability	0.105	0.322	0.126	0.237
Daytime diastolic BP variability	**0.297**	**0.004**	0.149	0.154
Nighttime diastolic BP variability	0.041	0.683	−0.069	0.503
24-hour diastolic BP variability	**0.203**	**0.048**	0.100	0.336
Daytime mean systolic BP	**0.351**	**0.001**	0.089	0.405
Nighttime mean systolic BP	**0.390**	**< 0.001**	0.087	0.409
24-hour mean systolic BP	**0.370**	**< 0.001**	0.090	0.402
Daytime mean diastolic BP	0.170	0.108	0.076	0.482
Nighttime mean diastolic BP	**0.241**	**0.019**	0.090	0.393
24-hour mean diastolic BP	0.193	0.068	0.079	0.461
Office systolic BP	**0.258**	**0.015**	0.068	0.531
Hypertension duration	**0.210**	**0.061**	0.114	0.316

BP, blood pressure.

variability. All regression models were adjusted for age, sex, smoking status, the presence of diabetes, body mass index, fasting glycemia and HbA1c values (Table 5).

4. Discussions

We hypothesized that elevated serum ICAM-1 and VCAM-1 might be a consequence of increased 24-hour ambulatory BP variability. It has been proven that serum ICAM-1 and VCAM-1 have an important role in the inflammation and activation of endothelial cells of the vascular walls [5,10], while increased BP variability is an independent cardiovascular risk factor as important as BP control [16,17]. Our data suggest that 24-hour ambulatory systolic and diastolic BP variability might play pathogenic role in endothelial dysfunction by increasing circulating adhesion molecules in patients with T2DM and controls. Previous studies indicated the positive associations between inflammatory serum biomarkers and increased BP variability [19–21]. To our knowledge, our observation is among the first reporting the association of increased high serum ICAM-1 with 24-hour ambulatory BP variability.

Increased 24-hour ambulatory BP variability and mean BP are known to be associated with cardiovascular disease [27]. In particular, nighttime systolic BP variability [28] and diastolic BP variability, but not daytime BP variability, were reported to be independent predictors of cardiovascular events in the presence hypertension and diabetes [28,29]. We found that nighttime systolic BP variability correlated with ICAM-1 in the study population, daytime diastolic BP variability correlated with VCAM-1 in patients with T2DM, while daytime and 24-hour ambulatory BP variability remained associated with ICAM-1, after adjusted for confounders, in the study population. To support the importance of BP variability, a recent meta-analysis reported that increased BP variability was associated with cardiovascular outcomes even in the presence of controlled mean BP [17]. Evidence from observational and interventional studies evaluating patients with diabetes and hypertension suggest that strategies aiming to reduce mean BP should also reduce the degree of BP variability in order to optimize cardiovascular protection [29].

Previous studies reported correlations between serum adhesion molecules and BP, while inconsistencies in the relationships are frequent depending on population characteristic and types of adhesion molecules evaluated [30]. We found that ICAM-1 was significantly correlated with mean systolic BP during daytime, nighttime and 24-hour periods in the study population, and also in the T2DM population. Both serum ICAM-1 and VCAM-1 were positively correlated with office systolic and diastolic BP in a study evaluation the effect of BP reduction on these two markers of endothelial cell activity or injury [31]. Recent studies reported significant correlation of VCAM-1 with ambulatory 24-hour and daytime systolic BP [32] and office diastolic BP [3]. In contrast to our findings, Miller et al reported no correlation between ICAM-1 or VCAM-1 and office BP in a population that did not include individuals treated for hypertension or diabetes [30].

The difference in ICAM-1 and VCAM-1 interaction with BP might relay in the different regulation by pro-inflammatory cytokines, or might be a consequence of the fact that adhesion molecules have each specific role in the adhesion pathway [30]. Though, we observed a significant correlation between the ICAM-1 and VCAM-1, possibly explained by the fact that both molecules are expressed on the surface of endothelial cells in response to tissue damage and inflammation [7]. The expression of endothelial adhesion molecules ICAM-1 and VCAM-1is related to leucocyte firm attachment and transmigration into the vascular subendothelial space, being a key step in atherogenesis [5,6]. Conversely, the hypothesis of possible protective effect of VCAM-1 on cardiovascular outcomes in patients without diabetes has been recently advanced following PREVEND study [6], in contrast with most studies supporting the role of VCAM-1 [33] and ICAM in cardiovascular disease [5,7].

The uncontrolled BP T2DM group had higher ICAM-1 and VCAM-1 compared to controlled BP T2DM and control groups. Previous studies reported the association of both ICAM-1 and VCAM-1 with the presence of newly diagnosed hypertension [3] and uncomplicated hypertension [11]. Decreased ICAM-1 and VCAM-1 levels were reported after BP reduction using anti-hypertensive medication, suggesting de-activation of endothelium with the reduction in BP [31].

Elevated adhesion molecules reflect alterations in the vascular endothelium and contribute to endothelial dysfunction. The inflammatory process evaluated by cell adhesion molecules levels associated with impaired vascular endothelial function in the presence of type 2 diabetes [1,8,10,11]. Our observation confirms that patients with T2DM from both controlled and uncontrolled BP groups had higher ICAM-1 and VCAM-1 compared to control group. Both ICAM-1 and VCAM-1 concentrations were higher in a study including patients with hypertension, diabetes and diabetes plus hypertension compared to normotensive peers [14]. Similar results were reported more recently for ICAM-1 in patients with diabetes [4,10]. Conversely, Boulbou et al found no differences in ICAM-1 and VCAM-1 levels when comparing patients with T2DM to persons with normoglycemia, while patients with hypertension had elevated VCAM-1, but not ICAM-1 compared to persons with normal BP [13].

The present study evaluated the association of cell adhesion molecules ICAM-1 and VCAM with 24-hour ambulatory BP monitoring and demonstrated the positive association of ICAM-1 with daytime systolic, daytime diastolic and 24-hour diastolic BP variability and the association of VCAM with daytime systolic BP variability. In turn,

inflammatory changes in the arterial wall indicated by increased cell adhesion molecules could worsen BP control and increase BP variability. Our cross-sectional study has certain limitations: the relatively small number of participants and the lack of evaluation of the vascular endothelial dysfunction using methods such flow-mediated vasodilatation.

5. Conclusions

Our study evaluating the association of serum ICAM-1 and VCAM-1 with 24-hour ambulatory BP variability in patients with type 2 diabetes and controls might offer better understanding of the mechanisms generating endothelial dysfunction. Elevated 24-hour ambulatory BP variability might induce endothelial activation by increasing circulating adhesion molecules levels, ICAM-1 and VCAM-1.

Declaration of interest

The authors declare that they have no conflict of interest.

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References

[1] B. Ruszkowska-Ciastek, A. Sokup, T. Wernik, Z. Ruprecht, B. Góralczyk, K. Góralczyk, G. Gadomska, D. Rość, Effect of uncontrolled hyperglycemia on levels of adhesion molecules in patients with diabetes mellitus type 2, J. Zhejiang Univ. Sci. B 16 (2015) 355–361, https://doi.org/10.1631/jzus.B1400218.
[2] C. Muntean, A. Mitrea, S. Popa, V. Tudorică, M. Moţa, Biochemistry of hyperglycemia induced vascular dysfunction, Rom. J. Diabetes Nutr. Metab. Disease 20 (2013) 419–425, https://doi.org/10.2478/rjdnmd-2013-0042.
[3] K.K. Shalia, M.R. Mashru, J.B. Vasvani, R.A. Mokal, S.M. Mithbawkar, P.K. Thakur, Circulating levels of cell adhesion molecules in hypertension, Indian J. Clin. Biochem. 24 (2009) 388–397, https://doi.org/10.1007/s12291-009-0070-6.
[4] R.M. Touyz, C. Savoia, Y. He, D. Endemann, Q. Pu, E.A. Ko, C. DeCiuceis, A. Montezano, E.L. Schiffrin, Increased inflammatory biomarkers in hypertensive type 2 diabetic patients: improvement after angiotensin II type 1 receptor blockade, J. Am. Soc. Hypertens. (2007) 189–199, https://doi.org/10.1016/j.jash.2007.01.009.
[5] M.D. Gross, S.J. Bielinski, J.R. Suarez-Lopez, A.P. Reiner, K. Bailey, B. Thyagarajan, J.J. Carr, D.A. Duprez, D.R. Jr, Jacobs, Circulating soluble intercellular adhesion molecule 1 and subclinical atherosclerosis: the coronary artery risk development in young adults study, Clin. Chem. 58 (2012) 411–420, https://doi.org/10.1373/clinchem.2011.168559.
[6] S.K. Kunutsor, S.J.L. Bakker, R.P.F. Dullaart, Soluble vascular cell adhesion molecules may be protective of future cardiovascular disease risk: findings from the PREVEND prospective cohort study, J. Atheroscler. Thromb. 24 (2017) 804–818, https://doi.org/10.5551/jat.38836.
[7] G. Luc, D. Arveiler, A. Evans, P. Amouyel, J. Ferrieres, J.M. Bard, L. Elkhalil, J.C. Fruchart, P. Ducimetiere, PRIME study group, circulating soluble adhesion molecules ICAM-1 and VCAM-1 and incident coronary heart disease: the PRIME study, Atherosclerosis 170 (2003) 169–176, https://doi.org/10.1016/S0021-9150(03)00280-6.
[8] A.R. Lenghel, I.M. Kacso, C.I. Bondor, C. Rusu, R. Rahaian, M. Gherman Caprioara, Intercellular adhesion molecule, plasma adiponectin and albuminuria in type 2 diabetic patients, Diabetes Res. Clin. Pract. 95 (2012) 55–61, https://doi.org/10.1016/j.diabres.2011.08.028.
[9] A. Blum, N. Pastukh, D. Socea, H. Jabaly, Levels of adhesion molecules in peripheral blood correlat with stages of diabetic retinopathy and may serve as bio markers for microvascular complications, Cytokine 106 (2018) 76–79, https://doi.org/10.1016/j.cyto.2017.10.014.
[10] M.E. Al-Ghurabi, A.A. Muhi, D.H. Al-Mudhafar, Vascular cell adhesion molecule-1 and endothelial leukocyte adhesion molecule-1 as markers of atherosclerosis of NIDDM, Am. J. Life Sci. 3 (2015) 22, https://doi.org/10.11648/j.ajls.20150301.15.
[11] C.A. DeSouza, D.R. Dengel, R.F. Macko, K. Cox, D.R. Seals, Elevated levels of circulating cell adhesion molecules in uncomplicated essential hypertension, Am. J. Hypertens. 10 (1997) 1335–1341.
[12] Z. Huang, C. Chen, S. Li, F. Kong, P. Shan, W. Huang, Serum markers of endothelial dysfunction and inflammation increase in hypertension with prediabetes mellitus, Genet. Test. Mol. Biomark. 20 (2016) 322–327, https://doi.org/10.1089/gtmb.2015.0255.
[13] M.S. Boulbou, G.N. Koukoulis, E.D. Makri, E.A. Petinaki, K.I. Gourgoulianis, A.E. Germenis, Circulating adhesion molecules levels in type 2 diabetes mellitus and hypertension, Int. J. Cardiol. 98 (2005) 39–44, https://doi.org/10.1016/j.ijcard.2003.07.037.
[14] D. Rizzoni, E. Porteri, D. Guelfi, M.L. Muiesan, A. Piccoli, U. Valentini, A. Cimino, A. Girelli, M. Salvetti, C. De Ciuceis, G.A. Tiberio, S.M. Giulini, I. Sleiman, C. Monteduro, E.A. Rosei, Endothelial dysfunction in small resistance arteries of patients with non-insulin-dependent diabetes mellitus, J. Hypertens. 19 (2001) 913–919.
[15] G. Parati, J.E. Ochoa, C. Lombardi, G. Bilo, Assessment and management of blood-pressure variability, Nat. Rev. Cardiol. 10 (2013) 143–155, https://doi.org/10.1038/nrcardio.2013.1.
[16] G. Leoncini, F. Viazzi, G. Storace, G. Deferrari, R. Pontremoli, Blood pressure variability and multiple organ damage in primary hypertension, J. Hum. Hypertens. 27 (2013) 663–670, https://doi.org/10.1038/jhh.2013.45.
[17] S.L. Stevens, S. Wood, C. Koshiaris, K. Law, P. Glasziou, R.J. Stevens, R.J. McManus, Blood pressure variability and cardiovascular disease: systematic review and meta-analysis, BMJ 354 (2016) i4098, , https://doi.org/10.1136/bmj.i4098.
[18] P. Verdecchia, F. Angeli, R. Gattobigio, C. Rapicetta, G. Reboldi, Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension, Am. J. Hypertens. 20 (2007) 154–161, https://doi.org/10.1016/j.amjhyper.2006.07.017.
[19] A. Tatasciore, M. Zimarino, G. Renda, M. Zurro, M. Soccio, C. Prontera, M. Emdin, M. Flacco, G. Schillaci, R. DE Caterina, Awake blood pressure variability, inflammatory markers and target organ damage in newly diagnosed hypertension, Hypertens. Res. 31 (2008) 2137–2146, https://doi.org/10.1291/hypres.31.2137.
[20] D.M. Ciobanu, C.G. Bala, I.A. Veresiu, P.A. Mircea, G. Roman, High-sensitivity C-reactive protein is associated with 24-hour ambulatory blood pressure variability in type 2 diabetes and control subjects, Rev. Rom. Med. Lab. 24 (2016) 65–73, https://doi.org/10.1515/rrlm-2016-0013.
[21] C. Jiangyan, L. Zhengliqiang, M. Lixiaodong, Association among systolic blood pressure variation, inflammation and arterial rigidity in essential hypertension, J. Hypertens. 4 (2015) 207, https://doi.org/10.4172/2167-1095.1000207.
[22] M. Ozawa, K. Tamura, K. Iwatsubo, K. Matsushita, M. Sakai, Y. Tsurumi-Ikeya, K. Azuma, A. Shigenaga, Y. Okano, S. Masuda, H. Wakui, T. Ishigami, S. Umemura, Ambulatory blood pressure variability is increased in diabetic hypertensives, Clin. Exp. Hypertens. 30 (2008) 213–224, https://doi.org/10.1080/10641960802068477.
[23] G. Parati, J.E. Ochoa, P. Salvi, C. Lombardi, G. Bilo, Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes, Diabetes Care 36 (2013) S312–S324, https://doi.org/10.2337/dcS13-2043.
[24] American Diabetes Association, 2. Classification and diagnosis of diabetes, Diabetes Care 36 (2013) S67–S74, https://doi.org/10.2337/dc13-S067.
[25] American Diabetes Association, 8. Cardiovascular disease and risk management, Diabetes Care 38 (2015) S49–S57, https://doi.org/10.2337/dc15-S011.
[26] G. Mancia, R. Fagard, K. Narkiewicz, J. Redón, A. Zanchetti, M. Böhm, T. Christiaens, R. Cifkova, G. De Backer, A. Dominiczak, M. Galderisi, D.E. Grobbee, T. Jaarsma, P. Kirchhof, S.E. Kjeldsen, S. Laurent, A.J. Manolis, P.M. Nilsson, L.M. Ruilope, R.E. Schmieder, P.A. Sirnes, P. Sleight, M. Viigimaa, B. Waeber, F. Zannad, Task Force Members, ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), Eur. Heart J. 34 (2013) (2013) 2159–2219, https://doi.org/10.1093/eurheartj/eht151.
[27] X. Ke, Y. Sun, R. Yang, J. Liang, S. Wu, C. Hu, X. Wang, Association of 24 h-systolic blood pressure variability and cardiovascular disease in patients with obstructive sleep apnea, BMC Cardiovasc. Disord. 17 (2017) 287, https://doi.org/10.1186/s12872-017-0723-y.
[28] M. Ozawa, K. Tamura, Y. Okano, K. Matsushita, M. Yanagi, Y. Tsurumi-Ikeya, J. Oshikawa, T. Hashimoto, S. Masuda, H. Wakui, A. Shigenaga, K. Azuma, T. Ishigami, Y. Toya, T. Ishikawa, S. Umemura, Identification of an increased short-term blood pressure variability on ambulatory blood pressure monitoring as a coronary risk factor in diabetic hypertensives, Clin. Exp. Hypertens. 31 (2009) 259–270, https://doi.org/10.1080/10641960902822518.
[29] P. Palatini, G. Reboldi, L.J. Beilin, E. Casiglia, K. Eguchi, Y. Imai, K. Kario, T. Ohkubo, S.D. Pierdomenico, J.E. Schwartz, L. Wing, P. Verdecchia, Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the ambulatory blood pressure-international study, Hypertension 64 (2014) 487–493, https://doi.org/10.1161/HYPERTENSIONAHA.114.03694.
[30] M.A. Miller, S.M. Kerry, D.G. Cook, F.P. Cappuccio, Cellular adhesion molecules and blood pressure: interaction with sex in a multi-ethnic population, J. Hypertens. 22 (2004) 705–711.
[31] R. Tadzic, M. Mihalj, A. Vcev, J. Ennen, A. Tadzic, I. Drenjancevic, The effects of arterial blood pressure reduction on endocan and soluble endothelial cell adhesion molecules (CAMs) and CAMs ligands expression in hypertensive patients on Ca-channel blocker therapy, Kidney Blood Press. Res. 37 (2013) 103–115, https://doi.org/10.1159/000350064.
[32] N. Pertseva, C. Daria, Endothelial dysfunction and 24-hour ambulatory blood pressure monitoring in patients with diabetes, Rom. J. Diabetes Nutr. Metab. Dis. 25 (2018) 141–147, https://doi.org/10.2478/rjdnmd-2018-0016.
[33] C. Schmidt, J. Hulthe, B. Fagerberg, Baseline ICAM-1 and VCAM-1 are increased in initially healthy middle-aged men who develop cardiovascular disease during 6.6 years of follow-up, Angiology 60 (2009) 108–114, https://doi.org/10.1177/0003319708316899.