Do components of metabolic syndrome contribute to cardiac autonomic neuropathy in non-diabetic patients?

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ABSTRACT

الأهداف: تقييم ظهور الاعتلال الذاتي في المرضى المصابين بمتلازمة الأيض و تأسيس أي صلة مع مكملات متلازمة الأيض (MetS).

الطريقة: حضر 32 مريض المركز الطبي السريري لجامعة زمن – بلقريد خلال الفترة من يوليو 2008م حتى يناير 2009م، حيث اشتملت الدراسة على 15 مريض مصاب بمتلازمة الأيض (MetS) و 17 مريض مصاب بالسكري (T2DM)، و الأفراد الأصحاء المماثلين بالعمر، و الجنس، بينما استبعدت فئة مرضى السكر غير المسيطر (الهيموجلوبين أعلى من9%)، أعراض السكر المتقدمة (اعتلال الشبكية، و اعتلال الكلية، و مرض القلب التاجي، و أمراض الأوعية المحيطية). تم تحليل مصل الجلوكوز، و الهيموجلوبين، و الجليسريد، و الكلويسترول، و HDL-C، كما أخذت اختبارات الانعكاس الذاتي للقلب الوعائية، و مراقبة تصوير القلب الكهربائي المتنقل، و مراقبة ضغط الدم لأربع و عشرين ساعة. أجري التحليل الطيفي للقوى لاختلاف معدل القلب بواسطة تحليل فوريه السريع.

النتائج: اشتمل معدل القوة الكلي (TP) على تردد منخفض، و تردد مرتفع و سجل انخفاض بشكل إحصائي في المرضى المصابين بالسكري (T2DM) عند مقارنتهم مع الأشخاص السليمين، و كانت القوة مرتفعة التردد منخفضة بشكل إحصائي مهم في المجموعة المصابة بمتلازمة الأيض. كانت نسبة القيمة المتوسطة للتردد المنخفض مرتفعة في المرضى المصابين بالسكري (T2DM) ومتلازمة الأيض (MetS). كانت القيمة المتوسطة للتردد المنخفض، والمتوسط أعلى في المرضى المصابين بالسكري والأيض (MetS)، ومتصل بمستوى الجلوكوز.

خاتمة: تدعم هذه النتائج فرضية التي تدل على اختلاف معدل القلب في الأشخاص المصابين بمتلازمة الأيض قبل تطور أعراض مرض السكر، وتطور مؤشرات الأيض، ومستوى الجلوكوز في البداية، واكتشاف اعتلال القلب الوظيفي الذي يجب أن يصبح واجب متساو مهم.

Objectives: To evaluate whether autonomic dysfunction exist in patients with metabolic syndrome (MetS) to establish any association with components of MetS.

Methods: From July 2008 to January 2009, 32 outpatients attending the University Clinical Center, Zemun, Belgrade, Serbia, 15 with MetS, 17 with type 2 diabetes mellitus (T2DM), and 15 control subjects were recruited for cross-sectional study among adults. The study was completed at the University Clinical Center, Bezanijska Kosa, and University Clinical Center, Dragisa Misovic, Belgrade, Serbia. Inclusion criteria were the presence of MetS without T2DM, T2DM and healthy controls, matched for age and gender. Exclusion criteria were uncontrolled diabetes (glycosylated hemoglobin [HbA1c] higher than 9%), advanced complications of diabetes (retinopathy, nephropathy, coronary heart disease, or peripheral angiopathy). Besides anthropometric and metabolic parameters cardiovascular autonomic reflex tests, ambulatory ECG monitoring, and blood pressure monitoring for 24 hours was obtained. Power spectral analysis of heart rate variability (HRV) was carried out by Fourier transformation.

Results: Mean total power (TP) log-transformed (ln), very low frequency (VLF)ln power, and high frequency (HF)ln power were significantly lower in T2DM patients, when compared with controls, and only HFln power was significantly lower in the MetS group. The average value of low frequency (LF)/HFln ratio was significantly higher in T2DM and MetS, and significantly correlated with glucose level of the last one.

Conclusion: Disturbed HRV indices were present in patients with MetS before the development of T2DM. With this in mind, improvement of glucose metabolism, as well as early detection of cardiac autonomic dysfunction should be important.

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The adverse effects of overweight, particularly in conjunction with metabolic disturbance identified as metabolic syndrome (MetS), represent major issues in health care.[1] A large proportion of obese subjects develop insulin resistance (IR), which represents an insensitivity of the peripheral tissues to the effects of insulin.[2,3] It is not only a major underlying mechanism in the development of type 2 diabetes mellitus (T2DM) associated with obesity,[4] but is also an independent cardiovascular risk factor. Metabolic syndrome (namely, IR syndrome) is defined as the clustering of several cardiovascular risk factors in an individual, including impaired glucose tolerance (or diabetes), hypertension, dyslipidemia, and visceral obesity.[5,6] Cross-sectional studies in adults without diabetes provide evidence that increased heart rate and diminished heart rate variability (HRV) are associated with obesity, IR, and fasting glucose (FG).[7,8] The findings of a longitudinal Norwegian study suggest the predictive role of sympathoadrenal activity in the development of IR.[9] A relation between IR and cardiac autonomic regulation has been identified in an experimental model: central infusion of an inhibitor of carnitine palmitoyltransferase-1 (CPT-1), which increases hypothalamic fatty acyl-CoA by reducing fatty acid (FA) oxidation, activates neurons in brain stem areas that control parasympathetic outflow and increased hepatic insulin sensitivity through a mechanism that involves activation of vagal efferent fibers that supply the liver.[10] Some studies demonstrated that the increase of plasma insulin level was related to increased urinary and plasma norepinephrine,[6] and other studies have shown that acute hyperinsulinemia increases sympathetic activity in muscle nerves.[7] Autonomic impairment has been observed at the time of diabetes diagnosis, which suggested that impairment may be present after a relatively brief exposure to hyperglycemia, or could develop in conjunction with obesity or IR.[8,9] Cross-sectional studies in adults without diabetes provide evidence that markers of autonomic functioning are inversely associated with obesity, IR, and FG.[10] Autonomic dysfunction may not only be one of the mechanisms by which MetS develops clustering of risk factors, but also contributes to the development of diabetes and cardiovascular diseases.[11] Recent research suggested that autonomic dysfunction (AD) may not only be the consequence of, but also a precursor to hyperglycemia, as seen in new-onset T2DM. However, it has been stated that AD did not precede development of the MetS, but appeared after syndrome components are present.[11] In addition, it is possible that both IR and autonomic dysfunction have a shared precursor, such as physical inactivity, or obesity, both of which are established risk factors for developing diabetes. This supports the long-held clinical suspicion that autonomic dysfunction is associated with the development of diabetes in healthy adults.[12-14] The aims of the present study are to test whether measures of autonomic function, such as HRV indices, were related to metabolic components of MetS and T2DM, and to establish the conceivable presence of disturbed circadian (diurnal) rhythms of HRV, and ambulatory blood pressure (AMBP) in these patients.

Methods. Patients in this adult cross-sectional study were recruited between July 2008 and January 2009 from the outpatient population of the Department of Endocrinology, University Clinical Center, Zemun, Belgrade, Serbia. All patients were under the care of the same endocrinologist. Blood tests for metabolic variables (glucose, glycosylated hemoglobin [HbA1c], triglycerides, cholesterol, high-density lipoprotein cholesterol [HDL-C]) were performed in all patients. Venous blood samples were obtained between 7 and 8 AM after an overnight fast. Patients then completed the study at the Department of Cardiology, Neuro-Cardiological Unit, University Clinical Center, Bezanijska Kosa, and the Cardiology Department, University Clinical Center, Dragisa Misovic, Belgrade, Serbia. All patients gave informed consent, and the Scientific Ethical Committee of the University Clinical Center, Zemun, Belgrade, Serbia approved the study.

Study population. We studied 32 consecutive patients, 15 with MetS (9 females, and 6 males; mean age - 57.63 ± 7.55 years), and 17 with T2DM (10 females and 7 males; mean age - 55.36 ± 4.63 years). The control group (15 persons) consisted of gender and age matched healthy subjects. The patients were selected carefully and referred from an endocrinologist to the Neuro-Cardiological Unit. All the examinees fulfilled the following inclusion criteria: the presence of MetS without diabetes; and T2DM, treated with oral anti-diabetic agents (ADA; [metformin and sulfonylurea]). The exclusion criteria included uncontrolled diabetes (HbA1c higher than 9%), advanced complications of diabetes (retinopathy, nephropathy, coronary heart disease, or peripheral angiopathy), and other serious co-morbidity, as well as age more than 65. All patients received optimal diet therapy, and those with dyslipidemia received hypolipemic agents, preferably fibrates. The diabetic patients were controlled with diet and oral ADA. Hypertension was mild and was treated with angiotensin converting enzyme (ACE) inhibitors only. The diagnosis of MetS was based on the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria.[15] Metabolic syndrome was defined by the presence of 3 or more of the following 5 factors: obesity (body mass index

[BMI] ≥25.0 and/or waist circumference according to the ATP III criteria); triglyceride 1.7 mmol/L or higher and/or treatment with fibrates; HDL-C lower than 1.29 mmol/L for women, and lower than 1.03 mmol/L for men; systolic blood pressure (SBP) 130 mm Hg or higher, diastolic (DBP) 85 mm Hg or higher, and/or on antihypertensive medication; and fasting plasma glucose (FPG) 5.6 mmol/L or higher.

Cardiovascular autonomic reflex tests. Ewing tests. A hand grip test, orthostatic hypotension (sympathetic function) and HRV during deep breathing, including expiration/inspiration ratio; maximum/minimum 30:15 ratio to standing up, and Valsalva ratio (parasympathetic function) was used to assess autonomic nerve function. According to Ewing et al[16] parasympathetic dysfunction was established if one of the 3 heart rate tests was abnormal or 2 were borderline; sympathetic dysfunction if at least one blood pressure test was abnormal, and total involvement of cardiac autonomic neuropathy (CAN) was recognized in cases where 2 or more of the heart rate tests were abnormal, and one or 2 blood pressure tests were abnormal.

Measurement of heart rate variability. Twenty-four hour ambulatory ECG monitoring was obtained in all patients using a 3-channel ECG Holter monitor (ArguSys, Budapest, Hungary). Electrocardiogram signals were digitized and stored using a commercially available PC-based system. Power spectral analysis of HRV was carried out by fast Fourier transformation. Heart rate variability is currently used as a tool for the assessment of equilibrium in the activity of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) in the control of heart rate. For the evaluation of HRV, the time domain and frequency domain analyses (power spectral analysis) were used. For time domain analysis, 2 HRV indices were measured: the standard deviation (SD) of all normal-to-normal RR intervals in the entire recording (SDNN) (milliseconds) and the square root of the average of sum of squares of difference between adjacent filtered RR intervals (rMSSD) (milliseconds). The SDNN represents joint sympathetic and parasympathetic modulation of heart rate, whereas rMSSD is thought to represent parasympathetic modulation of heart rate. From frequency domain analysis, 3 different frequencies were reported in addition to total power (TP); high-frequency (HF) power (0.15-0.4 Hz), low-frequency power (LF) power (0.04-0.15 Hz), and very low-frequency power (VLF) power (0.003-0.04). Low-frequency power is thought to reflect both sympathetic and parasympathetic activity, whereas HF is determined solely by parasympathetic activity. An LF/HFln ratio was calculated as a measure of sympathovagal balance that would reflect any shift toward sympathetic or parasympathetic activation.[17]

Measurement of ambulatory blood pressure. Ambulatory blood pressure monitoring (Custo screen Custo Med, GmbH, Ottobrunn, Germany) was performed for 24 hours with programmed readings every 15 minutes throughout the day (08:00-23:59 hours) and night (00:00-07:59 hours). Patients were asked to keep their arm still while the cuff was inflating, and to avoid excessive physical exertion during monitoring. The readings were downloaded into a computer at the end of the recording period, and standard protocols were used to evaluate ambulatory measurements. The average, maximal, and minimal values for diurnal, awake, asleep, and total 24-hour intervals were obtained. Normal mean values <135/85 mm Hg for the day interval, and <120/75 mm Hg for the night interval were accepted. According to JNC VII classification of hypertension, the average difference between walking and sleeping SBP and DBP is more than 10% in subjects with normotension or with hypertension.

Statistical analysis. Data are expressed as means ± SD. As the distribution of the HRV measurements was skewed to the right, the values were log-transformed and a normal distribution was confirmed by the Kolmogorov-Smirnov goodness of-fit test (p>0.15). Differences between groups were analyzed by general model analysis of variance (ANOVA), and post hoc multiple comparisons were performed using the least significant difference (LSD) test when ANOVA testing was significant (p<0.05). Significance of difference of proportions was made by reference to Finney's 2×2 contingency tables. Correlation analysis was performed by calculating Pearson's correlation coefficient. By stepwise multivariate linear regression analysis, we identified potential association between components of MetS and HRV measures. All statistical analyses were carried out with the Statistical Package for Social Sciences software package, Version 15.0, (SPSS Inc, Chicago, IL, USA). Statistical tests were all 2-sided (<0.05).

Results. Demographic characteristics and MetS features of the study patients as well as control subjects are shown in **Table 1**. The mean levels of BMI, and triglycerides were significantly higher in MetS patients compared with T2DM patients, and HbA1c was significantly lower in MetS patients than in the T2DM group. Almost half of the T2DM patients were treated with metformin, and the others were on combined treatment with metformin and sulfonylureas. The treatment choice of lipid lowering drugs, statins, and fibrates did not differ between the patients. The mean values of SBP and DBP and the presence of hypertension did not differ between the groups, but the application of ACE inhibitors was significantly higher in T2DM

patients than in controls (**Table 1**). We analyzed the results of autonomic testing in both groups of patients, and the presence of total AD, according to Ewing tests, did not differ between groups (42.9% (MetS group) versus 46.2% (T2DM group), p=0.63), as well as the presence of at least 2 positive tests for parasympathetic dysfunction (85.7% (MetS group) versus 71.4% (T2DM group), p=0.68). Sympathetic dysfunction was present almost as frequently in those with T2DM (42.9% versus 76.9% (MetS group), p=0.17). The results of short-term and long-term HRV indices are presented in **Table 2**. There was no significant difference between groups for any of the time domains. The mean TPln power, VLFln power, and HFln power were significantly lower in T2DM patients when compared with control subjects (on short-term ECG, and 24 hour ECG), and only HFln power was significantly lower in the MetS group (24 hour ECG). The mean value of LF/HFln ratio was significantly higher in patients with MetS, and T2DM, compared with controls, but did not differ between the patient groups (24 hour ECG). No differences existed between the 2 patient groups for any HRV measurement, except for VLFln power (24 hour ECG), where the T2DM value was significantly lower. The relationships between HRV indices, and anthropometric and metabolic variables in MetS patients are shown in **Table 3**. Glucose level correlated negatively with HFln power, and positively with LF/HFln ration as well as the LF/HFln asleep ratio. Stepwise multiple regression analysis was performed by using HRV indices, HFln power, LF/HFln ratio, and LF/HFln ratio asleep as dependent variables. After adjustment for gender, age, duration of disease, and metabolic variables, the independent predictor for HRV indices was only glucose level. The variance of glucose explained 36% of HFln power (p=0.006), 15% of LF/HFln ratio (p=0.05), and 32% of LF/HFln asleep (p=0.02). We analyzed the circadian rhythms of sympathovagal balance in the study groups. The value of LF/HFln ratio asleep was significantly lower than LF/HFln awake in the MetS group (0.76 versus 1.41, p=0.02), as expected. However, the value of LF/HFln asleep did not differ significantly from LF/HFln awake in the T2DM group (1.30 versus 1.48, p>0.05) (**Table 2**). The mean values of AMBPs, SBP, and DBP, did not differ between the patient groups (**Table 4**). There was a high percentage of non-dippers in the MetS and T2DM groups for SBP and DBP. The day:night ratio of SBP

Table 1 - Demographic, clinical, and laboratory data for metabolic syndrome (MetS) and type 2 diabetic patients.

Variables	Controls	MetS	Type 2 DM	*P*-value between Control and T2DM groups	*P*-value between MetS and T2DM groups
Number of participants (female)	15 (9)	15 (9)	17 (10)	0.19	0.09
Age, years	54.38 ± 8.30	57.63 ± 7.55	55.36 ± 4.63	0.47	0.30
Disease duration, mean (range) in years		3 (2-3)	4 (2-10)	0.18	0.18
Body mass index (kg/m^2)	26.59 ± 1.75	28.59 ± 0,75	27.77 ± 2.90)	0.23	0.02
Waist circumference(cm)	95.30 ± 7.55	97.43. ± 7.55	94.40 ± 13.0	0.27	0.27
Fasting glucose (mmol/L)	5.02 ± 0.54	6.02 ± 0.54	6.49 ± 1.14	0.01	0.06
HbA1c (%)	(4.90)	(6.10)	(7.20)	0.01	0.04
Oral anti-diabetics					
Metformin, (%)			(47)		
Metformin + Sulfonylureas, (%)			(53)		
Cholesterol (mmol/L)	5. 94 ± 0.74	6.54 ± 0.74	5.40 ± 0.79	0.81	0.21
HDL-cholesterol (mmol/L)	1.28 ± 0.34	1.17 ± 0.22	1.12 ± 0.37	0.06	0.76
Triglycerides (mmol/L)	1.55 ± 0.90	3.25 ± 1.35	2.13 ± 0.59	0.05	0.03
Lipid lowering drugs					
Statins, (%)		26.60	35.30	0.48	
Fibrates, (%)		53.33	29.40	0.20	
Systolic BP (mm Hg)	125.43 ±18.46	128.43 ±16.35	129.23 ± 15.52	0.72	0.52
Diastolic BP (mm Hg)	76.57 ± 5.76	78.47 ± 8.42	79.08 ± 12.13	0.78	0.69
Hypertension, (%)	(20)	(40)	(29.4)	0.51	0.19
Antihypertensive drugs					
ACE inhibitors, (%)	(60)	(80)	(100)	0.13	0.01

Values are mean ± standard deviation, unless otherwise stated. HbA1c -glycosylated hemoglobin, HDL - high-density lipoprotein, BP - blood pressure, ACE - angiotensin converting enzyme, T2DM - type 2 diabetes mellitus

Table 2 - Short term and 24-hour heart rate variability analysis in metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) patients.

Variables	Controls	MetS	Type 2 DM	*P*-value of Control group	*P*-values between Control and MetS groups	*P*-value of MetS and T2DM groups
Short term HRV						
LFRRIln	5.40 ± 0.69	5.36 ± 0.96	4.59 ± 1.05	0.71	0.89	0.87
VLFRRIln	6.09 ± 0.25	5.65 ± 0.76	4.75 ± 1.95	0.24	0.03	0.10
HFRRIln	6.94 ± 0.49	4.85 ± 1.24	3.98 ± 0.05	0.16	0.01	0.20
LF/HF RRIln	0.77 ± 0.05	0.51 ± 0.48	0.70 ± 0.38	0.64	0.93	0.78
24 hour HRV						
SDNNln	4.72 ± 0.44	4.87 ± 0.17	4.68 ± 0.28	0.37	0.78	0.13
rMSSDln	2.98 ± 0.93	3.28 ± 0.34	2.89 ± 0.43	0.31	0.72	0.31
Total powerln	7.51 ± 0.41	6.35 ± 0.99	5.56 ± 0.98	0.08	0.003	0.06
VLFRRIln	5.88 ± 0.75	5.65 ± 0.76	4.23 ± 1.33	0.88	0.005	0.01
LFRRIln	5.72 ± 0.82	5.36 ± 0.96	4.59 ± 1.05	0.43	0.08	0.07
HFRRIln	6.72 ± 0.89	4.85 ± 1.24	3.98 ± 1.37	0.002	0.001	0.80
LF/HFRRIln	0.99 ± 0.28	1.14 ± 0.23	1.36 ± 0.65	0.007	0.001	0.70
Sleep apnea						
LF/HF awake		3.50 ± 2.90-5.4	5.20 ± 2.50-7.5		0.90	
LF/HFln awake ln		1.41 ± 0.21	1.48 ± 0.33		0.31	
LF/HF asleep		2.20 ± 1.80-2.9	2.70 ± 2.00-4.7		0.15	
LF/HFln asleep ln		0.76 ± 0.12†	1.30 ± 0.33		0.16	
ΔLF/HF awake/asleep		1.40 ± 1.00-3.09	0.70 ± -1.60-1.9		0.50	
ΔLF/HFln Awake/asleepln		0.61 ± 0.30	0.26 ± 0.44		0.71	

Values are mean ± standard deviation (SD), or median (interquartile range); †p=0.02 in comparison to low frequency (LF)/high frequency (HF) log-transformed (ln) awake; LFRRI - low frequency component of R-R interval variability ln; VLFRRI - very low frequency component of R-R interval variability ln; HFRRI - high frequency component of R-R interval variability ln; SDNN - SD of all normal-to-normal RR intervals in the entire recording, milliseconds; rMSSD - square root of the average of sum of squares of difference between adjacent filtered RR intervals, milliseconds

Table 3 - Pearson's correlation coefficients between HRV indices and anthropometric and metabolic parameters of metabolic syndrome patients.

Variables	HFln	LFln	VLFln	LF/HFln	LF/HFln (asleep)
Age	0.253	-0.481†	0.155	-0.186	-0.321
Duration of disease	0.071	-0.385	0.057	-0.432*	-0.471*
Body mass index	-0.229	-0.165	0.058	0.072	-0.069
Waist cicumference	-0.293	-0.138	0.122	0.088	-0.257
Glucose	-0.633†	-0.364	-0.376	0.398*	0.605†
Triglycerides	-0.329	-0.040	-0.241	0.326	0.244
HDL-cholesterol	0.114	-0.006	0.133	-0.113	-0.051
Systolic blood pressure	0.359	-0.122	0.082	-0.367*	-0.258
Diastolic blood pressure	0.342	0.049	0.110	-0.346	-0.247

HRV - heart rate variability, MetS - metabolic syndrome, HDL - high density lipoprotein, HF ln - high frequency log-transformed, LF ln - low frequency ln, VLF ln - very low frequency, *significance of correlation (p<0.05), †significance of correlations (p<0.01).

was significantly higher in the MetS patients than in T2DM group. The SD of SBP asleep was significantly lower than the SD of SBP awake in both patient groups (**Table 4**).

Discussion. This study found that the presence of MetS in otherwise, healthy adults, was related to the presence of cardiovascular AD, according to standard cardiovascular autonomic reflex tests, and to impaired values of HRV indices. Disturbed sympathovagal balance with dominated parasympathetic dysfunction, according to HRV indices, was recorded in MetS group, as well as in T2DM patients.We could speculate that parasympathetic activity was reduced in both groups of patients, MetS and T2DM, and sympathovagal balance was shifted toward sympathetic predominance. The TPln power and VLFln power were lower only in T2DM patients, when compared with controls. This

could be the consequence of more serious impairment of sympathovagal balance in diabetic patients than in patients with MetS only. These results support the hypothesis that autonomic dysfunction is present in patients with MetS before the development of T2DM. Our results agree with those of Oda et al,[7] who clearly showed that the prevalence of MetS in a Japanese population increased linearly through the increase in heart rate. However, our study is cross-sectional, and we could not conclude whether autonomic dysfunction preceded the development of MetS and T2DM, or is a consequence of it. Flaa et al,[9] demonstrated that increased sympathetic activity is related to future IR in a follow-up study of 18 years. They found that the norepinephrine response to the cold pressor test at entry, independently predicted, or calculated insulin resistance index HOMA-IR.

The limitation of the study was the lack of fasting plasma insulin at entry. So, it is possible that those with greater sympathetic reactivity at baseline already had a higher level of IR. However, we have shown that fasting plasma glucose level could remain an independent predictor of abnormal HFln power, as well as LF/HFln ratio for the MetS group of patients, or conversely disturbed sympathovagal balance could be responsible for metabolic derangement, or hyperglycemia in the range of MetS. Huggett at al[18] reported the presence of sympathetic hyperactivity in offspring of T2DM, and stated that it occurred in proportion to the increased levels of plasma insulin and IR. These associations have been noted at first time, and the authors speculate 2 possible mechanisms. According to previous data, raised plasma insulin level and IR could lead to an increase in central sympathetic nerve output.[19] The reduction in HRV recorded in the MetS subjects may be explained by the underlying pathophysiology of MetS. Obesity and IR are acknowledged as essential factors in MetS.[1-3] Obesity is responsible for decreasing adiponectin, which is produced by adipose tissue, resulting in IR.[20] Insulin resistance, in turn, leads to an increased serum insulin level, which can activate the central sympathetic nervous system[19] via glucose metabolism in the ventral medial hypothalamus.Therefore, an increase in sympathetic activity could be associated with disturbed activity of the cardiac autonomic nervous system. Moreover, as suggested by Moller and Kaufman,[21] individuals with MetS have high levels of adipose tissue, atherogenic dyslipidemia, hypertension, and proinflammatory or prothrombotic events, each of which could be associated with cardiac autonomic imbalance. The results of the LINOSA study[22] have shown that baroreflex gain, but not spectrally derived indices of sinoatrial node autonomic regulation, are progressively reduced with increasing severity of IR, possibly as a consequence of attendant carotid artery thickening.

Our study also evaluates and compares the circadian autonomic rhythm measured by HRV, obtained by 24-hour ECG Holter registration in the same IR subjects with MetS and T2DM. We demonstrated that the sympathovagal balance (expressed by the LF/HFln ratio) remains consistently altered with a sympathetic over-activity during the night in diabetic subjects. The mean value of LF/HFln ratio was almost the same for the asleep as well as for the awake period in T2DM patients. In the MetS group, the LF/HFln ratio was almost twice lower during sleep, in accordance with the unimpaired circadian rhythm of autonomic activity for those subjects. We found lower day/night ratio for systolic BP in the T2DM group compared with the MetS group, in agreement with the state of worse circadian rhythm of systolic BP in T2DM patients. We also established higher presence of non-dippers in both groups of patients. In an experimental study, mice lacking a key component of the molecular circadian clock in the hypothalamus (Clock mutants) developed a MetS with hyperlipidemia, hepatic steatosis, and hyperglycemia.[23] Hyperinsulinemia, however, may increase BP by enhancing sodium reabsorption primarily at the distal nephron, an action that is independent of the hormonal effect on the sympathetic and renin-angiotensin-aldosterone system activities.[24]

Table 4 - Ambulatory blood pressure (BP) of the study population.

Parameters	MetS	Type 2 diabetes
24-hour ambulatory BP		
Systolic (S) BP, mm Hg	125.43 ± 18.46	129.23 ± 15.52
Diastolic (D) BP, mm Hg	76.57 ± 5.76	79.08 ± 12.13
Awake ambulatory BP		
SBP, mm Hg	128.86 ± 17.43	131.46 ± 14.79
DBP, mm Hg	77.71 ± 7.36	79.38 ± 12.17
SD of SBP, mm Hg	15.40 ± 5.98	16.65 ± 4.80
SD of DBP, mm Hg	12.11 ± 2.69	12.40 ± 5.72
Asleep ambulatory BP		
SBP mm Hg	112.71 ± 23.92	116.00 ± 14.53
DBP mmHg	67.57 ± 10.40	71.09 ± 6.47
SD of SBP, mmHg	11.38 ± 5.60*	11.39 ± 3.80*
SD of DBP, mmHg	8.16 ± 4.32	8.85 ± 2.92
Circadian variability		
Day:night ratio SBP	1.16 ± 0.13	1.11 ± 0.06†
Day:night ratio DBP	1.16 ± 0.12	1.07 ± 0.09
Non-dippers SBP (%)	(28.5)	(54.5)
Non-dippers DBP (%)	(28.5)	(63.6)

Values are mean ± standard deviation (SD) MetS - metabolic syndrome, *p=0.03 in comparation with SD of awake SBP; †p=0.04 for difference between groups

Non-dippers were recorded 3-5 times higher in the MetS and T2DM groups than in healthy subjects.[25] Reduced insulin sensitivity could be the cause, or potentate, AD with lower levels of day/night SBP ratio in T2DM subjects. This agrees with the established positive relationship between IR and hypertension in children and adolescents.[26]

The main study limitations are small sample size, and pharmacological treatment. The first limitation of our study was the lack of plasma insulin in the MetS group, and we could not establish an association between IR and HRV for those patients. The second is treatment of T2DM patients with metformin, partially responsible for IR improvement, and insulin secretagogs, sulfonylurea, which change the level of insulin, as well as progressive beta-cell failure, due to diabetes duration. It has been shown that co-treatment of dyslipidemia with fibrates in MetS and T2DM patients, can improve insulin action by decreased ectopic lipid content in the liver and muscle tissues,[27] and increased expression of adiponectin receptor 1 in adipose tissue, through activation of the peroxisome proliferator-activated receptor (PPAR) alpha.[28] The ACE inhibitors could also slightly improve insulin sensitivity in both groups of patients, and could be another limitation.[29] Our results agree with the statements of the ARIC study,[30] that AD was present at the early stages of metabolic disturbance and diabetic metabolic impairment was associated with a progressive worsening.

In conclusion, the results of the present study demonstrate the presence of AD in patients with MetS, even in type 2 diabetes. Glucose level, as a component of MetS, potentiates cardiac AD with sympathetic over-activity in patients without diabetes. These results support the hypothesis that reduced HRV, particularly HFln and increased LF/HFln, as a marker of autonomic dysfunction, are present in persons with MetS, before the development T2DM. Our results suggest that early detection of autonomic dysfunction should be equally important as well as screening of the MetS presence in non diabetic population. Future studies should provide new evidence, whether the treatment of AD and MetS components on time can improve cardiovascular outcomes.

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