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EDITED BY

Agata Stanek,
Medical University of Silesia, Poland

REVIEWED BY

Ewa Sadowska-Krepa,
Jerzy Kukuczka Academy of Physical
Education in Katowice, Poland
Grzegorz Jakubiak,
Medical University of Silesia, Poland

*CORRESPONDENCE

Attila Nemes
✉ attila.nemes.md@gmail.com

†These authors have contributed
equally to this work and share
last authorship

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A three-month physical training program improves cardiovascular autonomic function in patients with metabolic syndrome with and without diabetes – a pilot study

Anna Vágvölgyi¹, Judit Erzsébet Ábrahám²,
Éva Máthéné Köteles³, Andrea Korom³, Mária Barnai³,
Mónika Szűcs⁴, Andrea Orosz⁵, Péter Kempler⁶,
Adrienn Menyhárt⁶, Attila Nemes^{1*}, Tamás Várkonyi¹,
István Baczkó⁵, István Kósa^{1,2†} and Csaba Lengyel^{1†}

¹Department of Medicine, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary, ²Department of Medical Prevention, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary, ³Department of Physiotherapy, Faculty of Health Sciences and Social Studies, University of Szeged, Szeged, Hungary, ⁴Department of Medical Physics and Informatics, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary, ⁵Department of Pharmacology and Pharmacotherapy, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary, ⁶Department of Oncology and Internal Medicine, Semmelweis University, Budapest, Hungary

Introduction: Vascular complications and neuropathy may develop in the presence of metabolic syndrome. The aim of our study was to measure the cardiovascular autonomic function following physical training in patients with metabolic syndrome with and without diabetes.

Subjects and methods: 56 patients with metabolic syndrome (32 men/24 women, 40 non-diabetic patients (NDMetS)/16 diabetic patients (DMetS) [mean ± SD]: age: 50.35 ± 8.03 vs. 56.8 ± 9.30 years, p=0.023; baseline BMI: 32.2 ± 7.03 vs. 32.8 ± 5.94 kg/m², p=0.739) were involved in our study. All tests and measurements were carried out before and following a 3-month physical training period. Autonomic function was assessed by means of five standard cardiovascular reflex tests. ECG repolarization parameters, including short-term QT variability and stress-ECG were also measured.

Results: In the whole population, Valsalva-ratio (VR) and the autonomic score (AS) improved following training (VR: 1.49 ± 0.24 vs. 1.64 ± 0.34, p=0.001; AS: 2.05 ± 1.73 vs. 1.41 ± 1.36, p=0.015) accompanied by the significant decrease of the systolic (150.3 ± 16.12 vs. 134.1 ± 16.67 mmHg, p<0.001) and diastolic (90.64 ± 12.8 vs. 82.79 ± 11.1 mmHg, p<0.001) blood pressure. An improvement in VR was detected in NDMetS patients following training (1.51 ± 0.24 vs. 1.67 ± 0.31, p= 0.002). No significant changes could be detected in autonomic tests' results in the DMetS patient group following training. The applied exercise training program did not lead to significant changes in ECG repolarization. The stress-

ECG test in the whole study population yielded a significant increase in the test duration (12.9 ± 3.76 vs. 15.1 ± 2.96 min, $p < 0.001$) and in the test load (10.5 ± 2.78 vs. 11.6 ± 2.39 MET, $p < 0.001$). The load capability improved significantly in both subgroups: 11.1 ± 2.04 vs. 12.1 ± 1.82 , ($p < 0.001$) and 9.0 ± 3.64 vs. 10.4 ± 3.05 , ($p = 0.033$) in subpopulations of NDMetS and DMetS, respectively. The DMetS patients achieved a significantly lower MET score at baseline ($p = 0.039$) and following training ($p = 0.044$) in comparison to the NDMetS patients.

Conclusion: The three-month exercise program improved the Valsalva-ratio and the AN score in the MetS patients, that is potentially protective against cardiovascular events. The training had some beneficial effect on blood pressure and the results of the stress-ECG tests in both groups. The absence of significant change in the reflex tests in DMetS group reflects an impaired adaptation compared to the NDMetS group.

KEYWORDS

autonomic function, cardiovascular, diabetes, metabolic syndrome, physical exercise

Introduction

Obesity and its related consequences are associated with a significant health risk worldwide, and its management represents a huge financial burden both in the form of direct health care costs and social expenditures. Metabolic syndrome (MetS), a co-occurrence of abdominal obesity, dyslipidemia (elevated triglyceride levels and reduced high-density lipoprotein cholesterol) (1), hyperglycemia and hypertension, poses a major public health challenge. The current criteria for the diagnosis of metabolic syndrome include meeting at least three out of five previously mentioned conditions, which leads to a heterogeneity of the population of patients diagnosed with MetS. Among people with MetS might be present three to five components of metabolic syndrome, while there are patients with MetS with the same number, but different components of criteria for MetS. Jakubiak et al. have found that obesity and insulin resistance have been shown to be the component that contributes the most to the relationship between the metabolic syndrome and oxidative stress (2). Metabolic syndrome is expected to increase cardiovascular mortality by 1.8 times in the next 15 years (3), while another study predicts a two to fivefold increase in the risk of developing cardiovascular diseases and type 2 diabetes mellitus (T2DM) in the next 5 to 10 years (1). In developed countries, MetS affects around one fifth to one fourth of the population (4–6). In the prevention and treatment of MetS, lifestyle changes, especially regular physical exercise are recommended. In addition to aiming at the slowing and reversal of obesity-related pathological conditions, recently there has been an increased emphasis on the implementation of preventive measures.

The International Diabetes Federation (IDF) positions lifestyle intervention at the forefront of the treatment of metabolic syndrome as a primary intervention (7). Corresponding to this, IDF aims to increase physical activity, change dietary habits and

achieve a 5–10% reduction in body weight. Pharmacotherapy to reduce dyslipidemia, hypertension or insulin resistance should only be considered as a secondary intervention in cases where lifestyle interventions have failed (6).

Cardiovascular autonomic neuropathy (CAN) is defined as impaired autonomic control of the cardiovascular system, after the exclusion of other causes. CAN is a major complication of type 1 and type 2 diabetes mellitus; however, recent data suggest that CAN also occurs in obesity (8) and it is increasingly recognised in people with prediabetes and MetS, with a reported prevalence of up to 11% and 24%, respectively (9). CAN is associated with increased cardiovascular morbidity and the diagnosis of CAN is associated with a relative risk of mortality increase of at least 3.65 (10). CAN promotes ventricular repolarization disturbances that manifest as heart rate-corrected QT interval (QTc) prolongation and increased QT dispersion (QTd) on the ECG, both suggesting increased myocardial electrical instability, a substrate for fatal ventricular arrhythmias (11, 12).

Autonomic dysfunction and MetS in obese patients have been associated with normal glucose tolerance (NGT) and an increased prevalence of cardiovascular disease (13). A significant association has been shown between higher body mass index (BMI) and an elevated risk of CAN (14). In a randomized controlled trial, CAN was found to be associated with central obesity and impaired glucose tolerance with a prevalence of parasympathetic dysfunction observed in 25% of patients and a prevalence of sympathetic dysfunction observed in only 6% of patients (15).

In the obese population, calorie-controlled diet combined with regular exercise-based lifestyle interventions are crucial to prevent CAN (9, 16–18). Physical activity alone such as walking, moderate endurance and aerobic exercise demonstrated improvements in the cardiac autonomic function including heart-rate variability (19). Kluding et al. (20) published the first study, which described improvements in cutaneous nerve fiber branching following a

supervised 10-week aerobic and strengthening exercise program in people with diabetic peripheral neuropathy, in 2012. Furthermore, in T2DM patients, a significant improvement was detected in heart-rate variability following a 6-month long aerobic exercise-training program (21).

Máthéné Köteles et al. in 2023 (22) studied the physiological and psychological effects of a 12-week home-based and telemonitored physical exercise program in patients with metabolic syndrome. They involved 55 MetS patients who were instructed to perform 3–5 sessions of physical activity (at least 150 min) each week. Trainings were monitored off-line by heart rate sensors (smart watch or chest strap), and the data were transferred to an online platform by a fitness application through a cloud-based data transfer system, where physiotherapists supervised the training sessions giving weekly feedback to patients. The study revealed significant changes in several parameters, including waist and hip circumferences, 6-minute walking distance, maximal exercise capacity in METS, stress electrocardiogram duration time, body weight, and certain laboratory parameters such as HDL-cholesterol, fasting plasma glucose, and glycated hemoglobin A1c. Additionally, a notable reduction in the overall scores of the Maastricht Vital Exhaustion Questionnaire and an increase in the overall scores of the WHO Wellbeing Scale were also observed. They concluded that a 12-week home-based telemonitored training supported by an affordable and commonly available telemonitoring system could produce positive, statistically significant changes in many physical and psychological components in MetS patients.

There is little data in the literature regarding the effect of physical exercise on cardiovascular autonomic function and ECG parameters in patients with metabolic syndrome. Therefore, in the present study, we investigated whether our three-month-long home based exercise intervention program, supervised by remote patient monitoring, can improve cardiovascular autonomic nerve function. We also studied whether the training program had any effect on different ECG parameters that would suggest beneficial changes in repolarization instability, a known substrate for severe ventricular arrhythmias.

Subjects and methods

Subjects

Inclusion criteria

Metabolic syndrome is defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) MetS criteria (1, 23). Voluntary patients, aged between 25 and 70 years, were involved in the study, who practiced only low level of regular physical activity (self-reported, less than 30 min a week), and had at least three risk factors concomitantly from the followings (1, 23):

- waist circumference above 102 cm in men and above 88 cm in women,
- proved type 2 diabetes mellitus or FPG level above 5.6 mmol/L,

- treated hypertension or spontaneous blood pressure above 130/85 mmHg,
- treated hypertriglyceridemia or serum triglyceride level above 1.7 mmol/L,
- serum HDL (high-density lipoprotein) cholesterol level under 1.03 mmol/L in men, under 1.3 mmol/L in women.

Exclusion criteria

Participants were excluded with: any upcoming planned invasive cardiovascular intervention (percutaneous transluminal coronary angioplasty, coronary artery bypass, valve repair or replacement), chronic heart failure, uncontrolled hypertension (blood pressure > 160/100 mmHg), type 1 diabetes mellitus (T1DM), T2DM which needed more than one dose of insulin per day, chronic renal failure where the estimated Glomerular Filtration Rate < 60 ml/min/1.73 m², oncological diseases, serious cognitive dysfunction, lack of cooperation, any known disease or condition that seriously affected the mental and legal capacity, any other conditions preventing regular physical trainings.

The present study involved 56 patients diagnosed with metabolic syndrome [32 men/24 women, 40 non-diabetics (NDMetS)/16 diabetics (DMetS) {mean ± SD}: age: 50.35 ± 8.03 vs. 56.8 ± 9.30 years, p=0.023; baseline BMI: 32.2 ± 7.03 vs. 32.8 ± 5.94 kg/m², p=0.739]. Patients were monitored at the Department of Preventive Medicine, University of Szeged, Szeged, Hungary. The diabetic group consisted of patients with previously known diabetes or with HbA1c % above 6.5% in the baseline laboratory measurements.

All of the participants were of Caucasian origin. The relevant clinical data of MetS patients are shown in Table 1. Patients with NDMetS were significantly younger (50.4 ± 8.03 vs. 56.8 ± 9.30 years, p=0.023), presented with an elevated resting diastolic blood pressure (93.1 ± 13.54 vs. 84.6 ± 8.36 mmHg, P=0.007) and significantly fewer of them suffered from hypercholesterinemia as comorbidity (7 vs. 10, P=0.03). According to further biometrical parameters and medication-taking pattern, only anticoagulants and antidiabetics except insulin intake were significantly higher in the DMetS group. The medication of the subjects did not change during the examination period.

Intervention

Following the assessments, the participants were informed about the details and features of the exercise program and the monitoring procedures. They were requested to perform 3-5 training sessions (minimum 30 minutes/session), for a minimum of 150 minutes each week at home, for a total of 12 weeks. There were no restrictions regarding the type of training they performed, but patients were educated on the types and intensities of training recommended for individuals with metabolic syndrome, as outlined in the existing literature (24–26). The range of the training intensity was calculated based on the age dependent maximal heart rate (60–80%). Patients were also educated on the application of the chosen training monitor device and the procedures of the data transfer.

TABLE 1 Relevant baseline clinical data in the study groups.

	Non-Diabetic MetS Patients (n=40)	Diabetic MetS Patients (n=16)	P-value
Clinical Data			
Age (year)	50.4 ± 8.03	56.8 ± 9.30	0.023
Body Mass Index (BMI)	32.17 ± 7.03	32.8 ± 5.94	0.739
Waist-hip-ratio (WHR)	0.92 ± 0.11	0.94 ± 0.09	0.601
Male sex (%)	22 (55)	10 (63)	0.767
Systolic BP (mmHg)	150.8 ± 16.76	149.1 ± 14.8	0.724
Diastolic BP (mmHg)	93.1 ± 13.54	84.6 ± 8.36	0.007
Heart Rate (1/min)	73.44 ± 12.31	71.56 ± 10.96	0.583
Smoking history (%)	13 (33)	9 (56)	0.134
Alcohol consumption (%)	14 (35)	3 (19)	0.339
Hypertension (%)	25 (63)	11 (69)	0.763
Hypercholesterolemia (%)	7 (18)	10 (63)	0.003
Medication			
β-blocker (%)	11 (28)	7 (44)	0.343
ACE inhibitor or ARB (%)	20 (50)	11 (69)	0.245
Ca-antagonist (%)	9 (23)	7 (44)	0.189
Antidiabetics except insulin (%)	0 (0)	10 (63)	<0.001
Insulin (%)	0 (0)	2 (13)	0.078
Statin (%)	7 (18)	4 (25)	0.711
Diuretics (%)	15 (38)	6 (38)	0.999
ASA/PAI (%)	11 (28)	2 (13)	0.308
Anticoagulants	1 (3)	4 (25)	0.020

P-values below 0.05 level are marked bold. Values are presented as mean ± SD. BP, blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; Ca, calcium; ASA, acetylsalicylic acid; PAI, platelet aggregation inhibitor.

Home-based training sessions with remote patient monitoring

As many as 42 patients (10 with DMestS) participated in the home-based training sessions, which were monitored by two different types of devices. One of them was an electric heart rate sensor (Polar H10, Kempele, Finland) with a chest strap. Data collection was performed using a freely downloadable fitness application (Polar Beat) on a connected smartphone provided for the participants. At the end of the training session, the application automatically synchronized and transferred the data to a cloud based integrated system for online coaching (<https://flow.polar.com/coach>). The other type of device used was a smart watch with optical heart rate sensor (Polar M430 GPS running watch, Kempele, Finland). This watch was capable of initiating and stopping the training sessions. However, the data synchronization required, a patient-owned smart phone running the free to download Polar Flow fitness application or a patient-owned PC running the Polar Flow website. In this setting it was the patients' responsibility to initiate regular data upload using wireless connection of the smart phone or wired connection of the PC.

The patients performed their exercise program in their home environment while the physiotherapists provided offline monitoring and coaching for the training sessions, weekly contacting the patients *via* phone or email.

Supervised ambulatory training sessions

Fourteen patients (6 with DMestS) participated in the ambulatory supervised training group. These patients were scheduled for a 45-60-minute ambulatory training twice a week as well as a self-managed training session in their homes once a week. The ambulatory training sessions were supervised by physiotherapists. One of the two supervised training sessions was mainly a dynamic, endurance type training and consisted of a warm up period, followed by either ergometer cycling, treadmill run, or elliptical training and a cool down stage, altogether covering 60 minutes. The other session consisted of a resistance circle training including a warm up period, combined leg and arm exercises using the patients' own body weight, dumbbells and a cool down stage, also lasting for 60 minutes. During the supervised ambulatory training sessions, the subjects' heart rate was continuously

monitored with a chest strap Polar Team2 device (Kempele, Finland). This system allowed for simultaneous online monitoring of the heart rate of every person in the group, so the physiotherapist could continuously follow the whole group during the sessions. The third training of the week consisted of a home-based training session, self-managed and self-reported by the participants, and of a minimum 30-minute-long activity of their own choice.

Assessments

Ewing's five standard cardiovascular reflex tests, autonomic score

Autonomic neuropathy (AN), neuronal dysfunction and consequent cardiovascular changes were characterized with Ewing's five standard cardiovascular reflex tests (27) in the study. The Ewing-tests are the gold standards for diagnosing autonomic dysfunction; they provide non-invasive, clinically relevant, standardised and reproducible data of autonomic functions. Reflex tests were performed by measuring the blood pressure and obtaining continuous 6-lead ECG signals. The signals were digitised with a multichannel data acquisition system (Cardiosys-A01 software, MDE Heidelberg GmbH, Heidelberg, Germany), the sampling rate was 2 kHz and the data were stored for later analysis.

Three of these tests record heart rate changes when performing specific activities, while the rest measures changes in blood pressure. Tests, which record heart rate changes predominantly, reflect changes in parasympathetic function, while those based on blood pressure responses primarily describe sympathetic function disturbances (28). Heart rate changes were measured during deep inhalation and exhalation, in lying and standing positions with 30/15 ratio, and during and after Valsalva manoeuvre (10). Systolic blood pressure changes were measured after standing up from a lying position, while diastolic changes were recorded during gripping with the hand for 3 minutes.

CRT-s were scored separately: 0 (normal), 1 (borderline), 2 (abnormal). The overall autonomic score was calculated from the sum of each test result to characterise the severity of AN.

Heart rate response to deep breathing

Physiologically the heart rate increases on inhalation and decreases on exhalation. Patients were instructed to take deep breaths at a rate of six breaths per minute (inhale for five seconds and exhale for five seconds). The difference between the measured maximum and minimum heart rates (beats/min) was calculated during six cycles of breathing.

Heart rate response to standing up (30/15 ratio)

Normally, the heart rate increases promptly after standing up from a lying position and at about the 15th heartbeat after standing up, it reaches a peak. After that, relative bradycardia presents in healthy individuals with the lowest rate at around the 30th beat. Patients were lying in a supine position at the beginning of the test then they were asked to stand up while the ECG was recorded

continuously. The ratio of the longest R-R interval (around beat 30th) and the shortest R-R interval (around beat 15th) was calculated and recorded as the 30/15 ratio.

Heart rate response to the Valsalva manoeuvre (Valsalva-ratio)

In healthy individuals the blood pressure decreases and the heart rate increases during Valsalva manoeuvre. After the manoeuvre, the blood pressure increases and the heart rate decreases. Subjects were asked to exhale into a specific manometer through a mouthpiece and hold their breath at 40 mmHg for 15 seconds. During that period of time, ECG was continuously recorded. The ratio of the longest R-R interval following the test and the shortest R-R interval during the manoeuvre was calculated and recorded as the Valsalva-ratio.

Systolic blood pressure response to positional change (from lying to standing up)

Normally, in a standing position, the redistribution of blood to the lower limbs is immediately compensated by vasoconstriction in the peripheral vessels. Marked orthostatic hypotension is an important feature of cardiovascular consequences of neuropathy. The test is performed by measuring the blood pressure in a lying position and after standing up. An orthostatic drop in blood pressure is determined with systolic blood pressure measurements at 10 minutes after lying supine and at 1, 5 and 10 minutes after standing up. The difference between the values measured is noted and the largest difference is recorded as the response to standing up.

Diastolic blood pressure response during sustained handgrip

Changes in diastolic blood pressure were measured during sustained handgrip. At first, patients were asked to clamp a hand-held dynamometer with their dominant hand exerting full force so that we could determine the maximal grasping force, then they were instructed to maintain the grasp for 3 minutes at a constant, 30% force level. Blood pressure was measured once every minute on the contralateral, relaxed upper limb and the maximally increased diastolic blood pressure was recorded as the response to sustained handgrip.

12-lead electrocardiogram

All patients before and after the training exercise intervention were examined in the supine position following 5 minutes of rest. The 12-lead ECG was performed continuously for 10 minutes in the same position to avoid motion artefacts as much as possible. The ECG signal digitisation was performed with a multichannel data acquisition system (CAR03-IA, Cardiosys EXTRA software, MDE Heidelberg GmbH, Heidelberg, Germany), the sampling rate was 2 kHz and the data were stored for later analysis. All data acquired from subjects were appropriate for analysis. No data were excluded on the basis of exclusion criteria, which were the following: implanted pacemaker, several (>5%) ectopic atrial or ventricular beats, non-sinus rhythm, abnormal repolarization (i.e. early

repolarization, T-wave inversion, complete bundle branch block), acute metabolic disorder, significant artefacts in the ECG signal recording, high amount of food intake during the last 3 hours, alcohol or caffeine consumption or smoking during the last 10 hours. Repolarization was analysed based on the following parameters: frequency corrected QT interval (QTc) using Bazett ($QTc = QT/\sqrt{RR}$), Fridericia ($QTc = QT/[RR/1,000]^{1/3}$), Framingham ($QTc = QT + [0.154 \times \{1,000 - RR\}]$) and Hodges formulae ($QTc = QT + 1.75 \times [60,000/RR - 60]$), QT dispersion (QTd), terminal T-wave duration ($T_{peak} - T_{end}$), frequency corrected $T_{peak} - T_{end}$ interval using Bazett and Fridericia formulae and short-term variability of QT intervals (STV_{QT}). The RR and QT intervals, as well as the duration of the T wave from the peak to the end ($T_{peak} - T_{end}$) intervals were measured semi-automatically from 30 consecutive beats (minimum number of intervals needed for variability measurements) and were calculated as the average of 30 beats. Conventional computerised QT measurement technique was used for the analysis of QT intervals; blinded QT interval checking and if necessary, manual repositioning of the automatically set fiducial cursor were performed by the same investigator of the team (29). The duration of QTc interval was determined as the average of the measured QTc intervals. PQ and QRS intervals were determined as the average of the measured intervals of 15 consecutive beats. The measurements were performed in lead II or lead V5 if significant noise was present in the former. Poincaré plot analysis of the QT and RR intervals was performed to determine the temporal instability of the beat-to-beat heart rate (HR) and repolarization. Each QT and RR value was plotted against its former value. STV_{QT} and STV_{RR} were calculated using the following formula: $STV = \Sigma |D_{n+1} - D_n| (30 \times \sqrt{2})^{-1}$, where D represents the duration of the QT and RR intervals. The calculation defines the STV as the mean distance of points perpendicular to the line of identity in the Poincaré plot and relies on previous mathematical analysis (30).

Stress-electrocardiogram

Under the supervision of a cardiologist, a 12-channel electrocardiogram (CardioSys, MDE Diagnostic, Walldorf, Germany) was performed at rest and during exercise using an incremental loading in accordance with the Modified Bruce Protocol until the age-predicted maximal heart rate, where this target heart rate was calculated based on the 220-age formula. The maximal capacity in Metabolic Equivalent of Task (MET; ml/kg/min), the maximal heart rate (bpm), maximal systolic and diastolic blood pressure (mmHg) and the duration of stress-electrocardiogram test in minutes were measured and documented.

Statistical analysis

Data are reported as the mean \pm SD; or as frequencies (n) and percentages (%), when appropriate. Independent samples t-test and Fisher exact test were used for the comparison the baseline clinical data in the study groups. Repeated measures variance analysis (RM-ANOVA) was applied for the analysis cardiovascular autonomic

function tests (Table 2) and of ECG parameters (Table 3) before and after physical training where the grouped variables were the diabetic and non-diabetic subgroups. For pairwise comparisons, Bonferroni correction was used. Statistical tests were performed using R statistical software (R version 3.6.1), values of $p < 0.05$ were considered significant. Prior power analysis using the statistical software G-Power (Version 3.1.9.7) calculated an optimal total sample size of $N=52$, with an effect size $f=0.3$, alpha as Type I error of 0.05 and a power of 0.85.

Results

The three-month training program was considered effective, which was demonstrated by a significant decrease of the BMI from $32.4 \pm 6.67 \text{ kg/m}^2$ to $31.8 \pm 6.76 \text{ kg/m}^2$ ($p=0.008$). The weekly training activity duration was $155.4 \pm 113.5 \text{ min}$ in the undivided population. There was no significant difference in the duration of the weekly training activity between the NDMetS and DMetS subgroups: $165.7 \pm 117.95 \text{ min}$ vs. $137.6 \pm 94.91 \text{ min}$; $p=0.412$.

Cardiovascular autonomic function tests before and following the 3-month training program

The results of the cardiovascular autonomic function tests before and following the 3-month training program are shown in Table 2. In the whole population VR and the autonomic score improved significantly following the training (VR: 1.49 ± 0.24 vs. 1.64 ± 0.34 , $p=0.001$; AS: 2.05 ± 1.73 vs. 1.41 ± 1.36 , $p=0.015$, respectively) accompanied by significant decreases in the resting systolic (150.3 ± 16.12 vs. $134.1 \pm 16.67 \text{ mmHg}$, $p < 0.001$) and diastolic (90.64 ± 12.8 vs. $82.79 \pm 11.1 \text{ mmHg}$, $p < 0.001$) blood pressures.

SBPRSU following the training in the whole population also showed an improvement tendency, but the degree of change did not reach the level of statistical significance (6.95 ± 8.57 vs. $4.89 \pm 8.10 \text{ mmHg}$, $p=0.055$).

Considering the subgroups, a significant improvement in VR was detected in the NDMetS patients following training (1.51 ± 0.24 vs. 1.67 ± 0.31 , $p=0.002$), but no significant change could be detected in the autonomic test results in the DMetS patient group.

At baseline, the diabetic subpopulation demonstrated significantly impaired results on the HRRDB test in comparison to NDMetS patients: 17.12 ± 6.01 vs. 22.05 ± 8.56 ($p=0.019$). No further significant differences in the results of autonomic tests could be detected between the two subpopulations at either the baseline or the second measurement.

Similar to the entire population, there was a significant reduction in resting systolic and diastolic blood pressure (BP) in both the NDMetS (systolic BP: 152.0 ± 16.56 vs. $132.7 \pm 16.82 \text{ mmHg}$, $p < 0.001$; diastolic BP: 91.4 ± 13.28 vs. $83.2 \pm 11.14 \text{ mmHg}$, $p=0.001$, respectively) and the DMetS groups (systolic BP: 146.1 ± 14.62 vs. $137.7 \pm 16.26 \text{ mmHg}$; $p=0.024$; diastolic BP: 88.8 ± 11.68 vs. $81.8 \pm 11.30 \text{ mmHg}$, $p=0.002$, respectively).

TABLE 2 Results of the cardiovascular autonomic function tests before and following the 3-month training program in all patients (n=56) and with sub-analysis in non-diabetic (NDMetS; n=40) and in diabetic (DMetS; n=16) patients.

Cardiovascular Reflex Tests	Before training all patients (n=56)	Following training all patients (n=56)	Before Training NDMetS (n=40)	Following Training NDMetS (n=40)	Before Training DMetS (n=16)	Following Training DMetS (n=16)	P-value All patients before vs. following training	P-value NDMetS before vs. following training	P-value DMetS before vs. following training	P-value 1.M. DMetS vs. NDMetS	P-value 2.M. DMetS vs. NDMetS
HRRDB (1/min)	20.6 ± 8.17	22.3 ± 8.52	22.1 ± 8.56	23.1 ± 8.64	17.1 ± 6.01	20.3 ± 8.13	0.109	0.407	0.081	0.019	0.258
VR	1.5 ± 0.24	1.6 ± 0.34	1.5 ± 0.24	1.7 ± 0.31	1.4 ± 0.23	1.6 ± 0.40	0.001	0.002	0.189	0.336	0.411
HRRSU	1.1 ± 0.13	1.1 ± 0.12	1.1 ± 0.12	1.1 ± 0.13	1.2 ± 0.15	1.2 ± 0.10	0.698	0.542	0.721	0.256	0.504
SBRSU (mmHg)	6.9 ± 8.57	4.9 ± 8.10	6.4 ± 7.13	4.4 ± 7.48	8.4 ± 11.57	6.2 ± 9.61	0.055	0.126	0.259	0.509	0.506
DBPRH (mmHg)	17.3 ± 16.06	17.8 ± 11.77	18.2 ± 16.81	17.9 ± 12.40	14.8 ± 14.22	17.6 ± 10.37	0.824	0.903	0.432	0.448	0.945
Autonomic score	2.1 ± 1.73	1.4 ± 1.36	1.9 ± 1.58	1.4 ± 1.37	2.6 ± 2.03	1.5 ± 1.37	0.015	0.11	0.059	0.221	0.76
Systolic BP (mmHg)	150.3 ± 16.12	134.1 ± 16.67	152.0 ± 16.56	132.7 ± 16.82	146.1 ± 14.62	137.7 ± 16.26	<0.001	<0.001	0.024	0.198	± 0.313
Diastolic BP (mmHg)	90.6 ± 12.80	82.8 ± 11.1	91.4 ± 13.28	83.2 ± 11.14	88.8 ± 11.68	81.8 ± 11.3	<0.001	0.001	0.002	0.467	0.685

P-values below 0.05 level are marked bold. Values are presented as mean ± SD. 1.M. first measurement; 2.M. second measurement; HRRDB, the heart rate response to deep breathing; VR (Valsalva-ratio), the heart rate response to Valsalva maneuver; HRRSU (30/15 ratio), the heart rate responses to standing up; SBRSU, the systolic blood pressure response to standing up; DBPRH, the diastolic blood pressure response during sustained handgrip; BP, blood pressure.

ECG parameters before and following the 3-month training program

Comparing ECG parameters in all MetS patients revealed no significant differences in heart rate, the PQ, QRS and QT intervals and the QT dispersion. Furthermore, significant differences in the QTc values calculated with the Bazett, Fridericia, Framingham and Hodges formulae and the beat-to-beat short-term temporal variability of the QT interval were not identified (Table 3). The resting ECG parameters did not show any significant differences between the diabetic and non-diabetic subpopulations at baseline. After 3 months of training, significant changes were documented only in T_{peak} - T_{end} parameter in DMetS subjects before vs. following training (p=0.043) and following subanalysis of baseline values between the DMetS and NDMetS groups (p=0.027). As T_{peak} - T_{end} is heart rate dependent, a correction was applied with Bazett and with Fridericia formulae. The above mentioned significant differences in T_{peak} - T_{end} following frequency correction with Bazett and Fridericia formulae could not be verified.

Stress-electrocardiogram parameters before and following the 3-month training program

The exercise capacity of patients, as indicated by the duration of the stress-electrocardiogram test and the load values performed, exhibited a significant increase in the entire study population (12.9 ± 3.76 vs. 15.1 ± 2.96 min, p<0.001 and 10.5 ± 2.78 vs. 11.6 ± 2.39 MET, p<0.001) (Table 4). The DMestS patients achieved a significantly lower MET score at baseline (p=0.039) as well as following the training (p=0.044) in comparison to the NDMetS patients. The increase of MET value was consequent both in the NDMetS (11.1 ± 2.04 vs. 12.1 ± 1.82, p<0.001) and in the DMetS (9.0 ± 3.64 vs. 10.4 ± 3.05, p=0.033) subpopulations.

The maximal systolic BP achieved during the stress-electrocardiogram test was significantly lower in the DMetS group compared to the NDMetS group at the baseline (185.8 ± 31.95 vs. 211.2 ± 18.84 mmHg, p=0.01) and also following the training program (180.3 ± 20.57 vs. 206.1 ± 19.82 mmHg, p<0.001).

Discussion

Diabetic cardiovascular autonomic neuropathy (CAN) is defined by the Toronto consensus panel as “the impairment of autonomic control of the cardiovascular system in the setting of diabetes after the exclusion of other causes” (8, 31). CAN is widely recognized as a complication of type 1 and type 2 diabetes mellitus but there is growing evidence that CAN also occurs in patients with obesity, prediabetes or metabolic syndrome, preceding the development of T2DM (7). The population affected by CAN is, therefore, likely to grow as the obesity epidemic continues (16, 32–35). A study in patients with obesity and normal glucose tolerance has demonstrated that increased waist to hip ratio – indicating

TABLE 3 ECG parameters of all patients (n=56) and subgroups before and following the 3-month training program in diabetic (DMetS; n=16) and non-diabetic (NDMetS; n=40) patients evaluated by RM-ANOVA: pairwise comparisons with Bonferroni corrections.

ECG Parameters	Before training all patients (n=56)	Following training all patients (n=56)	Before Training NDMetS (n=40)	Following Training NDMetS (n=40)	Before Training DMetS (n=16)	Following Training DMetS (n=16)	P-value All patients before vs. following training	P-value NDMetS before vs. following training	P-value DMetS before vs. following training	P-value 1.M. DMetS vs. NDMetS	P-value 2.M. DMetS vs. NDMetS
HR (1/min)	72.7 ± 11.83	72.71 ± 9.91	73.5 ± 12.30	72.3 ± 8.77	70.8 ± 10.69	73.7 ± 12.58	0.999	0.481	0.104	0.412	0.696
RR (ms)	846.7 ± 137.40	842.6 ± 124.82	839.1 ± 140.06	843.6 ± 108.12	865.8 ± 132.94	840.3 ± 163.47	0.783	0.813	0.285	0.51	0.941
QT (ms)	401.5 ± 33.49	403.4 ± 33.40	398.3 ± 31.97	403.7 ± 30.59	409.6 ± 36.84	402.7 ± 40.72	0.555	0.187	0.129	0.295	0.927
QTc Bazett (ms)	438.2 ± 21.67	440.8 ± 22.54	436.9 ± 20.86	440.6 ± 23.37	441.6 ± 23.94	441.3 ± 21.04	0.246	0.178	0.952	0.500	0.912
QTc Fridericia (ms)	425.3 ± 21.11	427.8 ± 22.91	423.3 ± 19.44	427.8 ± 23.25	430.4 ± 24.79	427.7 ± 22.76	0.231	0.078	0.389	0.319	0.988
QTc Framingham (ms)	425.1 ± 20.09	427.7 ± 21.68	423.1 ± 18.23	427.8 ± 22.03	430.2 ± 24.02	427.3 ± 21.50	0.206	0.062	0.32	0.296	0.935
QTc Hodges (ms)	423.8 ± 20.90	425.5 ± 22.58	421.9 ± 18.83	425.1 ± 21.79	428.5 ± 25.43	426.5 ± 25.16	0.34	0.15	0.539	0.357	0.841
PQ (ms)	159.2 ± 19.83	160.9 ± 19.39	158.8 ± 21.82	159.0 ± 21.89	159.9 ± 15.01	165.1 ± 11.55	0.212	0.924	0.013	0.834	0.194
QRS (ms)	99.3 ± 16.08	99.3 ± 15.46	98.9 ± 16.52	98.6 ± 15.80	100.2 ± 15.43	100.9 ± 14.96	0.987	0.815	0.740	0.788	0.621
T _{peak} -T _{end} (ms)	87.4 ± 16.05	87.1 ± 15.68	84.5 ± 15.69	87.4 ± 16.24	94.9 ± 14.91	86.3 ± 14.66	0.865	0.170	0.043	0.027	0.795
T _{peak} -T _{end} (ms) Bazett	95.5 ± 16.18	95.0 ± 15.31	96.1 ± 17.34	95.7 ± 15.80	93.9 ± 13.31	93.2 ± 14.39	0.803	0.854	0.866	0.605	0.576
T _{peak} -T _{end} (ms) Fridericia	92.7 ± 15.80	92.2 ± 15.18	93.2 ± 17.00	92.9 ± 15.87	91.3 ± 12.79	90.4 ± 13.68	0.813	0.896	0.820	0.657	0.570
QTd	38.3 ± 10.88	39.7 ± 15.32	38.0 ± 10.98	37.4 ± 12.33	39.1 ± 10.96	45.4 ± 20.39	0.477	0.764	0.212	0.734	0.156
STV _{RR}	16.5 ± 18.72	15.01 ± 17.44	13.9 ± 12.56	14.1 ± 13.37	23.2 ± 28.43	17.3 ± 25.34	0.269	0.870	0.086	0.224	0.634
STV _{QT}	4.6 ± 1.10	4.5 ± 1.33	4.5 ± 1.19	4.4 ± 1.10	4.7 ± 0.89	4.9 ± 1.78	0.883	0.520	0.637	0.625	0.348

P-values below 0.05 level are marked bold. Values are presented as mean ± SD. 1.M, first measurement; 2.M, second measurement; HR, heart rate; QTc, frequency corrected QT interval (calculated by the Bazett, Fridericia, Framingham and Hodges formulas); T_{peak}-T_{end}, duration of the T wave from the peak to the end; T_{peak}-T_{end} Bazett/Fridericia, frequency corrected T_{peak}-T_{end} calculated by the Bazett, Fridericia formulas; QTd, QT dispersion; STV_{RR}, beat-to-beat short-term temporal variability of the RR interval; STV_{QT}, beat-to-beat short-term temporal variability of the QT interval.

TABLE 4 Stress-Electrocardiogram parameters of all patients (n=50) and subgroups before and following the 3-month training program in diabetic (DMetS; n=15) and non-diabetic (NDMetS; n=35).

Stress-Electrocardiogram Parameters	Before training all patients (n=50)	Following training all patients (n=50)	Before Training NDMetS (n=35)	Following Training NDMetS (n=35)	Before Training DMetS (n=15)	Following Training DMetS (n=15)	P-value All patients before vs. following training	P-value NDMetS before vs. following training	P-value DMetS before vs. following training	P-value 1.M. DMetS vs. NDMetS	P-value 2.M. DMetS vs. NDMetS
Duration (min)	12.9 ± 3.76	15.1 ± 2.96	13.3 ± 3.56	15.6 ± 2.51	11.9 ± 4.13	13.8 ± 3.56	<0.001	<0.001	0.009	0.231	0.083
Maximal exercise capacity (MET score)	10.5 ± 2.78	11.6 ± 2.39	11.1 ± 2.04	12.1 ± 1.82	9.0 ± 3.64	10.4 ± 3.05	<0.001	<0.001	0.033	0.039	0.044
Maximal heart rate	162.6 ± 25.67	161.0 ± 24.87	164.7 ± 24.62	161.9 ± 21.74	157.7 ± 28.08	159.0 ± 31.52	0.702	0.505	0.892	0.395	0.745
Maximal systolic BP (mmHg)	203.6 ± 26.01	198.4 ± 23.16	211.2 ± 18.84	206.1 ± 19.82	185.8 ± 31.95	180.3 ± 20.57	0.180	0.228	0.534	0.010	<0.001
Maximal diastolic BP (mmHg)	89.1 ± 12.04	86.4 ± 11.28	90.6 ± 12.35	87.5 ± 11.75	85.5 ± 10.88	84.0 ± 10.04	0.166	0.183	0.654	0.160	0.294

P-values below 0.05 level are marked bold. Values are presented as mean ± SD. 1.M, first measurement; 2.M, second measurement; BP, blood pressure.

visceral adiposity – is associated with impaired parasympathetic and sympathetic nervous system control of cardiac autonomic function (36). There is also a significant association between increasing body mass index (BMI) and an increased risk of CAN (14). An early diagnosis of CAN should be established wherever possible since it enables timely implementation of lifestyle and pharmacological interventions aimed at reversing CAN (10, 37). As suggested by the American Diabetes Association (ADA) position statement for diabetic neuropathy, the prevention of CAN is considered the optimal approach for avoiding its adverse consequences (16). Structured lifestyle intervention is recommended already for individuals with impaired fasting glucose or impaired glucose tolerance combined as they are at high risk for developing T2DM, and this approach is likely to reduce CAN (14, 38).

In the present study cardiovascular functional test results in non-diabetic patients with metabolic syndrome were found to be similar to those in patients with diabetic metabolic syndrome. At baseline, only the results of the HRRDB in the diabetic subpopulation showed significant impairment compared to NDMetS patients. This finding confirms an impaired parasympathetic cardiovascular autonomic function at baseline in comparison to the NDMetS group. A three-month training program with remote patient monitoring increased the Valsalva-ratio in the whole group, which provides strong evidence that the condition of the cardiovascular autonomic system can be improved through such a training program. The improvement of the Valsalva-ratio confirms the reinforcement of the parasympathetic tone, which is potentially protective against cardiovascular events. The absence of a significant change in the cardiovascular reflex tests following the training in the DMetS patient group suggests a more seriously impaired adaptation compared to the NDMestS subpopulation of patients with metabolic syndrome.

The systolic blood pressure response to positional change (from lying to standing up) showed a tendency towards improvement in the whole MetSy-population following the training program. It may be speculated that the current study was underpowered to document this change and a study with a larger sample size may be necessary to confirm the potential beneficial effect of physical training on the orthostatic counter regulation.

No further significant differences in autonomic test results could be detected between the two subpopulations at the baseline as well as following training. However, it is worth considering that the duration of diabetes documented in our study population was relatively short, with an average duration of 7.6± 8.12 years, which might explain the absence of a more severe CAN in diabetic individuals with MetS.

A state of sympathetic activation is associated with increased heart rate (39) and appears to promote cardiac and vascular alterations (40, 41), contributing to the development of major complications of hypertension such as arrhythmia, left ventricular hypertrophy and increased arterial stiffening (40–42). It was demonstrated that physical activity such as moderate endurance and aerobic exercise can improve autonomic function as assessed by the heart rate variability (HRV) analysis on the resting ECG (19). Significant improvements in HRV indices were demonstrated in

patients with T2DM following a 6-month aerobic exercise training program consisting of 3 training sessions per week. In that study, the subgroup of diabetic patients with definite CAN showed greater improvements in response to a 6-month exercise program compared to the diabetic patients without CAN (21). Michou et al. recently published a study investigating the effects of training on cardiac autonomic neuropathy and metabolic profile in patients with diabetes undergoing hemodialysis. They revealed a positive correlation between peak oxygen uptake and standard deviation of R-R intervals and heart rate after exercise training, which may be an indicator of improved cardiorespiratory efficiency levels affecting cardiac autonomic nervous system function (43). The type and quality of the monitoring and coaching services utilized may be important factors in determining the effectiveness of exercise intervention programs (44). Large, randomized trials in patients with prediabetes and the MetS comprising multifactorial and lifestyle interventions are advocated to establish the effectiveness of different prevention and treatment strategies for patients with prediabetes and CAN (8, 19). Population-based studies demonstrate that there is a higher proportion of deaths - consistent with sudden cardiac death - in CAN patients (19, 45). The mechanisms responsible for increased SCD include an increased incidence of silent myocardial ischaemia and also the prolongation of repolarization possibly leading to severe ventricular arrhythmias and cardiac arrest (46). Thirty years ago Ewing et al. showed in patients with diabetes that the resting QTc correlated with the developmental stage of CAN. They also reported that the resting QTc was longest in individuals who died unexpectedly in follow-up, possibly due to severe cardiac arrhythmias (47).

In the present study no differences were found in the analyzed ECG parameters (including QTc) between the DMetS and NDMetS subgroups at baseline or after a 3-month training period. The resting ECG parameter changes before and after training were significant only in $T_{\text{peak}}-T_{\text{end}}$ at the diabetic subgroup ($p=0.043$) and at baseline between the DMetS and NDMetS groups ($p=0.027$). This significant difference following frequency correction with Bazett and Fridericia formulae could not be verified. Furthermore, a three-month long exercise intervention program did not show any effect on the ECG parameters, suggesting its lack of effect on ventricular repolarization.

At the stress-electrocardiogram test in the whole study population, a significant increase of the duration and of the MET score was observed. In addition, a significant improvement was found by the subanalysis of the MET value in the NDMetS and in the DMetS subpopulation. The DMetS patients achieved a significantly lower MET score at baseline and following the training in comparison to the NDMetS patients. Additionally, the DMetS group showed a significantly lower maximal systolic BP during the stress-electrocardiogram test compared to the NDMetS group at baseline and at the second measurement following the training. This finding may be attributed to the stricter and more regular blood pressure control that diabetic patients receive as part of their diabetes care. Regardless of the presence of diabetes in patients with metabolic syndrome, the significant improvement observed in the stress-electrocardiogram and cardiovascular reflex tests following lifestyle-changing exercise therapy underscores its importance and effectiveness

as a treatment tool for these patients. The exercise training program applied in the study did not lead to significant changes in ECG repolarization parameters, including QT variability in both diabetic and non-diabetic patients with metabolic syndrome, but the effect of more rigorous intervention should be evaluated.

In summary, the three-month long exercise program improved the Valsalva-ratio and the autonomic score in the MetS patients, confirming the reinforcement of the parasympathetic tone, which is potentially protective against cardiovascular events. The absence of a significant change in the cardiovascular reflex tests following the training in the DMetS patient group suggests a more seriously impaired adaptation compared to the NDMetS subpopulation of patients with metabolic syndrome. The training had some beneficial effect on blood pressure and on the results of the stress-ECG tests in both groups. The exercise training program applied in the study did not lead to significant changes in ECG repolarization parameters, including QT variability in both diabetic and non-diabetic patients with metabolic syndrome, but the effect of more rigorous intervention should be evaluated optimally also in a larger sample size. Further studies need to address the effect of more rigorous exercise protocols with preferably longer duration on the investigated parameters.

Limitations

In the present study, the home based training was followed by a commercially available system, which is affordable and accessible for widespread utilization. The text message based coaching, included in this system was, however, not suitable for every patient involved, so we used telephone calls and emails to coach the patients. Unfortunately, we were not able to document the regularity and intensity of this coaching activity, which can obviously influence the outcome of the intervention. In subsequent studies, these issues will be addressed. A greater sample size is required to increase the statistical power of the study and allow for a more comprehensive investigation of the relationship between the intensity, extent and type of training and the achieved changes in the neuropathic status. Moreover, further research is warranted to investigate the effect of additional lifestyle interventions including nutrition coaching, on neuropathy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the Hungarian Medical Research Council (approval No. 50780-2/2017EKU). All subjects have given written informed consent of the study. As a clinical trial our study is also registered at ClinicalTrials.gov (identifier: NCT05146076).

Author contributions

AV, JÁ, ÉM, AK, MB, AO, PK, AN, TV, IB, CL and IK given substantial contributions to the conception, the methodology, and the design of the manuscript. JÁ given substantial contribution in the patient recruitment, selection, and data collection. AV, ÉM, AK, MB, IB and IK taken part in the investigation, data collection and the interpretation of the results. MS did the statistical analysis. AV participated in writing and drafting the manuscript. AV, ÉM, AN, PK, AM, TV, IB, CL and IK revised the manuscript critically. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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