

Original paper

Positive impact of a 4-week duration supervised aerobic training on anthropometric, metabolic, hemodynamic and arterial wall parameters in metabolic syndrome subjects

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Summary

Objectives: Metabolic syndrome (MetS) is linked to the development of type 2 diabetes and increased risk of cardiovascular disease (CVD). Physical inactivity is one of the main pathophysiological factors of MetS subjects. The aim of this study was to evaluate if 4-week supervised aerobic training had any impact on anthropometric, metabolic, hemodynamic and arterial wall parameters in MetS subjects.

Design and methods: 57 MetS subjects were randomly selected from a Lithuanian High Cardiovascular Risk (LitHiR) national primary prevention programme. Hemodynamic, cardiometabolic risk and arterial wall parameters were evaluated after the 4-week supervised aerobic training.

Results: After 4 weeks of aerobic training there was statistically significant decrease in body mass index from 30.58 ± 3.7 to 30.3 ± 3.55 kg/m² ($p = 0.010$), waist circumference from 104.24 ± 9.46 to 102.9 ± 9.48 cm ($p = 0.003$), decrease of LDL cholesterol from 4.21 ± 1.15 to 3.78 ± 1 mmol/l ($p = 0.032$) and high sensitivity C-reactive protein from 2.01 ± 2.36 to 1.64 ± 1.92 mg/l ($p = 0.009$), decrease of diastolic blood pressure (BP) from 83.06 ± 10.18 to 80.38 ± 8.98 mmHg ($p = 0.015$), mean BP from 100.03 ± 10.70 to 97.31 ± 8.88 mmHg ($p = 0.027$) and aortic stiffness, assessed as carotid-femoral pulse wave velocity, from 8.34 ± 1.26 to 7.91 ± 1.15 m/s ($p = 0.034$).

Conclusions: In subjects with MetS even short-duration (4-week) supervised aerobic exercise training is associated with improvement of some anthropometric, metabolic and hemodynamic parameters as well as the decrease in aortic stiffness. This training modality could be recommended for initiation of physical training and could increase motivation for further physical activity.

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Keywords: metabolic syndrome, physical inactivity, supervised aerobic exercise training, aortic pulse wave velocity

Introduction

Metabolic syndrome (MetS) subjects have a 5-fold increased risk of diabetes [1,2] and 3-fold increase of cardiovascular disease (CVD) mortal-

ity compared to the individuals without MetS [2]. The role of physical inactivity and obesity is growing in the development of CVD and type 2 diabetes mellitus (T2DM) [3,4]. According to the results of Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme, the incidence of MetS in the middle-aged population in Lithuania is 28.7% [5]. Sedentary lifestyle was found in 49.9% (in 54.4% of women and in 43.1% of men) of these subjects [6].

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Although the positive effect of aerobic activity in improvement of cardiovascular health is well accepted, the European Society of Cardiology has concluded that it has not yet been established how much exercise is required in order to improve the lipid profile and reduce cardiovascular risk [7].

Pathological changes of arterial wall parameters – arterial stiffness and carotid intima-media thickness – have been demonstrated to be prognostic markers for future cardiovascular events [8]. Changes of anthropometric, metabolic and arterial wall parameters occurring after supervised aerobic physical training could contribute to dynamic assessment of cardiovascular risk in MetS subjects and significantly enhance the motivation of these subjects for physically active lifestyle and physical training. Most of the previously conducted physical training interventional studies in MetS patients lasted 8 weeks and more [9–11]. Furthermore, none of them have compared the effects that occur as early as after 4 weeks of the supervised aerobic exercise training.

Objectives

The main purpose of this study was to evaluate if short 4-week duration supervised aerobic exercise training has any influence on metabolic syndrome parameters (anthropometric, metabolic) and to analyse dynamics of arterial wall parameters after training in metabolic syndrome subjects without overt diabetes mellitus and cardiovascular disease.

Design and methods

Study population

Our study subjects were randomly recruited from the participants of LitHiR (Lithuanian High Cardiovascular Risk) national primary prevention programme [3,5] between 2009 and 2014. The study prospectively included 57 individuals with MetS diagnosed on the basis of updated NCEP ATP III criteria [12].

All participants were physically inactive – performing less than 150 min/week of the moderate intensity physical training. The mean age of the subjects in the study was 52.79 ± 6.65 years, among them were 31 (54.4%) females and 26 (45.6%) males. Arterial hypertension was present in 53 (93%) of subjects. Dyslipidaemia was present in 55 subjects (96.5%), among them elevated LDL cholesterol (LDL-Chol) was present in 50 subjects (91%), elevated triglycerides (TG)

in 36 (65.5%), decreased HDL cholesterol (HDL-Chol) in 27 (49.1%) subjects. There were 50 (87.7%) patients with central obesity and 28 (49.1%) cases of fasting dysglycaemia.

The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all subjects.

Clinical assessment

The evaluation of anthropometric parameters and metabolic profile included weight, body mass index (BMI), waist circumference, blood pressure, venous blood samples for blood lipid levels, fasting glucose, high sensitivity C-reactive protein (hsCRP) as well as the arterial wall parameters assessed prior to and after 4-week of supervised aerobic physical training. All laboratory tests and arterial wall parameters were obtained at rest in the morning after an overnight fast.

Supervised aerobic physical training protocol

The 4-week exercise training protocols were applied. Specifically, the training intervention consisted of a 4-week duration supervised aerobic training for 30–40 min/day, 5 days/week. Exercise intensity was gradually increased from 40% to 60% of heart rate reserve (HRR). HRR is the difference between maximum heart rate and resting heart rate. Heart rate reserve was used to calculate heart rate exercise zones by the Karvonen Formula [13,14]. The ERS-2 Ergoline bicycle system (Ergoline GmbH) allowing to control the exercise load was used for the titrated exercise training.

Arterial wall parameters

Noninvasive assessment of arterial wall parameters was carried out by measuring aortic and peripheral arterial stiffness, and the common carotid artery intima-media thickness prior to and after the 4-week exercise training. Aortic and arterial stiffnesses were assessed by an applanation tonometry system (SphygmoCor v.8.0; AtCor Medical) [15]. Measurements of carotid–femoral pulse wave velocity (cfPWV in m/s, so-called aortic stiffness), carotid–radial pulse wave velocity (crPWV in m/s, so-called peripheral artery stiffness) and aortic augmentation index (AIxHR@75, %) were performed before and after the supervised aerobic training.

Common carotid intima media thickness (cIMT, μm), carotid artery distensibility and nondimensional index Quality Carotid Stiffness (QCS) of common carotid artery (CCA) [16] were measured using a high-resolution echo-tracking system (Art. Lab, Esaote Europe B.V.).

Statistical methods

Statistical analysis was performed using STATISTICA 10. Data were checked for normality using Shapiro–Wilk test. Differences between baseline and follow-up measurements were tested with paired Student's t-test or Wilcoxon signed-rank test, as appropriate. All *p* values were two-tailed and the level of significance was set to 0.05.

Results

Training-induced changes of anthropometric parameters and metabolic profile

The 4-week duration supervised aerobic physical training was associated with a statistically significant ($p < 0.05$) decrease in weight, BMI, waist circumference, LDL-Chol and hsCRP (Table 1).

Training-induced changes of hemodynamic and arterial wall parameters

The 4-week duration supervised aerobic physical training was associated with a statistically significant ($p < 0.05$) decrease of diastolic and mean BP but not systolic pressure.

We analysed the dynamics of arterial wall parameters by comparing them before and after training – aortic stiffness (cfPWV, m/s), and peripheral artery stiffness (crPWV, m/s), augmentation index (AIxHR@75, %), carotid stiffness (QCC) and carotid intima-media thickness (cIMT, μm). Statistically significant decrease of aortic (cfPWV) stiffness was found in the study group. Peripheral (crPWV) artery stiffness showed the tendency of diminishing but it did not reach the statistical significance. Changes in carotid stiffness (QCS) and carotid intima-media thickness (cIMT) was not observed in our cohort at all (Table 2).

Table 1.
Training-induced changes of anthropometric and biochemical parameters

Parameter	4-week training		
	Baseline	After training	<i>p</i> -value
Weight, kg	89.28 ± 14.04	88.52 ± 13.21	0.008
BMI, kg/m ²	30.58 ± 3.7	30.3 ± 3.55	0.010
Waist, cm	104.24 ± 9.46	102.9 ± 9.48	0.003
Total-Chol, mmol/L	6.42 ± 1.24	5.94 ± 1.63	0.063
LDL-Chol, mmol/L	4.21 ± 1.15	3.78 ± 1.26	0.032
HDL-Chol, mmol/L	1.12 ± 0.25	1.14 ± 0.27	0.928
TG, mmol/L	2.61 ± 2.72	2.26 ± 1.91	0.339
Fasting glucose, mmol/L	5.65 ± 0.46	5.65 ± 0.52	0.704
hsCRP, mg/L	2.01 ± 2.36	1.64 ± 1.92	0.009

BMI – body mass index, HDL-Chol – high density lipoprotein cholesterol, hsCRP – high sensitivity C-reactive protein, LDL-Chol – low density lipoprotein cholesterol, TG – triglycerides, Total-Chol – total cholesterol.

Table 2.
Hemodynamic and arterial parameters

Parameter	4-week training		
	Baseline	After training	<i>p</i> -value
Heart rate, b/min.	63.24 ± 8.02	61.96 ± 9.06	0.332
Systolic BP, mmHg	133.96 ± 14.01	131.19 ± 11.47	0.129
Diastolic BP, mmHg	83.06 ± 10.18	80.38 ± 8.98	0.015
Mean BP, mmHg	100.03 ± 10.70	97.31 ± 8.88	0.027
PWV radial, m/s	9.37 ± 1.49	8.94 ± 1.46	0.113
PWV femoral, m/s	8.34 ± 1.26	7.91 ± 1.15	0.034
AIxHR@75, %	22.17 ± 12.12	19.06 ± 3.72	0.080
IMT, μm	622.03 ± 82.62	639.17 ± 75.86	0.066
Carotid stiffness	4.04 ± 1.53	4.07 ± 1.26	0.495

AIxHR@75 – aortic augmentation index, BP – blood pressure, IMT – intima-media thickness, PWV – pulse wave velocity.

Discussion

The growing prevalence of obesity and increased incidence of MetS, that are considered to be precursors of T2DM and CVD, become a problem in the world [17,18]. Sedentary lifestyle is the predominant risk factor in subjects with MetS [19–22]. One of the most effective tools to prevent the manifestation and development of MetS is improving the adherence to physical activity. The lack of motivation for starting the measures that improve physical fitness and continuing physical activity for a long time is the major problem in MetS subjects. Furthermore, the optimal modality and duration of physical training needed to improve the metabolic profile and reduce cardiovascular risk is not yet established [7]. Various modalities of physical training – aerobic, aerobic interval, strength – are used in MetS subjects [10,23,24]. Since previous studies usually implemented 8 or more week duration training programmes in these subjects [9–11,25], we assessed if short 4-week duration supervised aerobic physical training could have some initial impact on anthropometric, metabolic, hemodynamic and arterial wall parameters in MetS subjects. We have demonstrated that short-duration supervised aerobic physical training improves anthropometric parameters, metabolic profile, and arterial wall parameters, and could serve as the initial step for continuous improvement of physical activity. Training-induced reversal of arterial wall stiffness would result in a decrease of cardiovascular risk in these subjects and additionally motivate MetS subjects to continue with physically active lifestyle.

After 4 weeks of moderate intensity supervised aerobic training we already observed the decrease of body weight, body mass index and abdominal circumference. These findings could motivate subjects with MetS to continue their physical activity.

We also observed the lowering of LDL-Chol that was present in the 4-week training group of subjects with MetS. The tendencies of decrease in TG and increase in HDL-Chol were likewise observed but they did not reach statistical significance. Most investigators could find the decrease of TG and the increase of HDL-Chol as prevalent changes in MetS subjects after physical training [26–30,29]. It was shown that if elevated LDL-Chol was present prior to the study, intensive physical training was decreasing it [27,29]. In our study 46 subjects (81%) also had elevated LDL-Chol prior to the physical training programme. C-reactive protein is also directly related to manifestation of atherosclerosis [31]. We were able to show a statistically significant decrease of

CRP after the 4-week aerobic training. Similar results in subjects with impaired glucose tolerance and obesity were presented by Andersson et al. [32].

The changes of arterial wall function and structure occurring prior to the development of obstructive atherosclerotic disease have been thoroughly studied over the last decades and are considered to be the precursors of developing overt CVD [33–35]. These changes can be assessed non-invasively by measuring the arterial stiffness and intima-media thickness. The golden standard for arterial stiffness evaluation is considered to be applanation tonometry performed by Sphygmocor, which allows to measure carotid-femoral PWV and carotid-radial PWV [15]. Sphygmocor-based measurements were chosen by us as the best validated method for evaluation of arterial function.

The assessment of arterial stiffness using Sphygmocor before and after 8 weeks of heart rate controlled physical training in 22 MetS patients was performed by Donley et al. [9]. The improvement of aortic and peripheral arterial stiffness parameters after exercising was shown in this study. We included a bigger cohort of subjects with MetS into our study and for the first time analysed the effect of a 4-week supervised aerobic exercise training on arterial wall parameters. We were able to show that the aortic stiffness (cfPWV) parameter is already improving after 4 weeks of supervised aerobic physical training. Other authors studied the effect of various modalities of physical activities – walking, jogging, incremental shuttle walk test – in metabolic, obese, diabetic subjects, and the results of these studies are contradictory [36–38].

Likewise, in our assessment of the carotid artery wall, we used the method superior to the one employed by the relevant studies published so far [39,40] – measurement of carotid artery distensibility and early structural change. Carotid artery intima-media thickening in μm was measured using the most advanced method of high-resolution echo-tracking by Artlab technology [16].

Conclusions

To conclude, in subjects with metabolic syndrome, a 4-week duration supervised aerobic exercise training (1) decreased body weight, body mass index and abdominal circumference, (2) improved lipid profile by lowering LDL-Chol and hsCRP, and (3) decreased aortic stiffness assessed by carotid-femoral pulse wave velocity; the latter seemed to be the most sensitive parameter for

monitoring of arterial wall function under aerobic physical training.

These early occurring positive changes can motivate the patient with metabolic syndrome to start physical training with a short-duration supervised aerobic training programme and then continue it at home.

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References

- [1] Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. *Diabetes Care* 2008;31(9):1898–904.
- [2] Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004;110(10):1245–50.
- [3] Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW 3rd, Blair SN. Reduction in cardiovascular disease risk factors: 6-month results from Project Active. *Prev Med* 1997;26(6):883–92.
- [4] Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012;380(9838):219–29.
- [5] Laucevičius A, Rinkūnienė E, Skujaitė A, Petrulionienė Ž, Purnaitė R, Dženkevičiūtė V, et al. Prevalence of cardiovascular risk factors in Lithuanian middle-aged subjects participating in the primary prevention program, analysis of the period 2009–2012. *Blood Press* 2015;24:41–7.
- [6] Egidija Rinkūnienė. The identification of patients at high-risk of cardiovascular disease and the optimization of methods of active primary prevention [in Lithuanian]. PhD thesis, Vilnius University, 2014.
- [7] Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Z, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. *Eur J Prev Cardiol* 2012;19(5):1005–33.
- [8] Scuteri A, Najjar SS, Orru' M, Usala G, Piras MG, Ferrucci L, et al. The central arterial burden of the metabolic syndrome is similar in men and women: the SardiNIA Study. *Eur Heart J* 2010;31(5): 602–13.
- [9] Donley DA, Fournier SB, Reger BL, DeVallance E, Bonner DE, Olfert IM, et al. Aerobic exercise training reduces arterial stiffness in metabolic syndrome. *J Appl Physiol* (1985). 2014;116(11):1396–404.
- [10] Mora-Rodríguez R, Ortega JE, Hamouti N, Fernandez-Elias VE, Cañete Garcia-Prieto J, Guadalupe-Grau A, et al. Time-course effects of aerobic interval training and detraining in patients with metabolic syndrome. *Nutr Metab Cardiovasc Dis* 2014;24(7):792–8.
- [11] Landaeta-Díaz L, Fernández JM, Da Silva-Grigoletto M, Rosado-Alvarez D, Gómez-Garduño A, Gómez-Delgado F, et al. Mediterranean diet, moderate-to-high intensity training, and health-related quality of life in adults with metabolic syndrome. *Eur J Prev Cardiol* 2013;20(4):555–64.
- [12] NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. *Circulation* 2002;106:3143–421.
- [13] Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bitner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 2013;128(8):873–934.
- [14] Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001;37(1):153–6.
- [15] Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Gannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27(21):2588–605.
- [16] Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J* 2013;34(30):2368–80.
- [17] Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015;313(19):1973–4.
- [18] Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Mañas LR, et al. Metabolic syndrome across Europe: different clusters of risk factors. *Eur J Prev Cardiol* 2015; 22(4): 486–491.
- [19] Ekblom Ö, Ekblom-Bak E, Rosengren A, Hallsten M, Bergström G, Börjesson M. Cardiorespiratory fitness, sedentary behaviour and physical activity are independently associated with the metabolic syndrome, results from the SCAPIS pilot study. *PLoS One* 2015;10(6):e0131586.
- [20] Greer AE, Sui X, Maslow AL, Greer BK, Blair SN. The effects of sedentary behavior on metabolic syndrome independent of physical activity and cardiorespiratory fitness. *J Phys Act Health* 2015;12(1):68–73.
- [21] Edwardson CL, Gorely T, Davies MJ, Gray LJ, Khunti K, Wilmot EG, et al. Association of sedentary behaviour with metabolic syndrome: a meta-analysis. *PLoS One* 2012;7(4):e34916.
- [22] Kim D, Yoon SJ, Lim DS, Gong YH, Ko S, Lee YH, et al. The preventive effects of lifestyle intervention on the occurrence of diabetes mellitus and acute myocardial infarction in metabolic syndrome. *Public Health* 2016;139:178–82.
- [23] Huffman KM, Sun JL, Thomas L, Bales CW, Califf RM, Yates T, et al. Impact of baseline physical activity and diet behavior on metabolic syndrome in a pharmaceutical trial: results from NAVIGATOR. *Metabolism* 2014;63(4):554–61.
- [24] Hansel B, Bonnefont-Rousselot D, Orsoni A, Bittar R, Giral P, Roussel R, et al. Lifestyle intervention enhances high-density lipoprotein function among patients with metabolic syndrome only at normal low-density lipoprotein cholesterol plasma levels. *J Clin Lipidol* 2016;10(5):1172–81.
- [25] Katzmarzyk PT, Leon AS, Wilmore JH, Skinner JS, Rao DC, Rankinen T, et al. Targeting the metabolic syndrome with exercise: evidence from the HERITAGE Family Study. *Med Sci Sports Exerc* 2003;35(10):1703–9.
- [26] Durstine JL, Grandjean PW, Cox CA, Thompson PD. Lipids, lipoproteins, and exercise. *J Cardiopulm Rehabil* 2002;22(6):385–98.

- [27] Gordon B, Chen S, Durstine JL. The Effects of Exercise Training on the Traditional Lipid Profile and Beyond. *Curr Sports Med Rep* 2014;13(4):253–9.
- [28] Ho SS, Dhaliwal SS, Hills AP, Pal S. The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. *BMC Public Health* 2012;12:704.
- [29] Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports Med* 2014;44(2):211–21.
- [30] Pattyn N, Cornelissen VA, Eshghi SR, Vanhees L. The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome. *Sports Med* 2013;43(2):121–33.
- [31] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135–1143.
- [32] Andersson J, Boman K, Jansson JH, Nilsson TK, Lindahl B. Effect of intensive lifestyle intervention on C-reactive protein in subjects with impaired glucose tolerance and obesity. Results from a randomized controlled trial with 5-year follow-up. *Biomarkers* 2008;13(7):671–9.
- [33] Nilsson PM. Early vascular aging (EVA): consequences and prevention. *Vasc Health Risk Manag* 2008;4(3):547–552.
- [34] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55(13):1318–27.
- [35] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007;115(4):459–67.
- [36] Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. *Am J Physiol* 1994;266:H693–701.
- [37] Radhakrishnan J, Swaminathan N, Pereira NM, Henderson K, Brodie DA. Acute changes in arterial stiffness following exercise in people with metabolic syndrome. *Diabetes Metab Syndr* 2016;11:237–43.
- [38] Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2014;9(10):e110034.
- [39] Cheng HG, Patel BS, Martin SS, Blaha M, Doneen A, Bale B, et. al. Effect of comprehensive cardiovascular disease risk management on longitudinal changes in carotid artery intima-media thickness in a community-based prevention clinic. *Arch Med Sci* 2016;12(4):728–35.
- [40] Jhamnani S, Patel D, Heimlich L, King F, Walitt B, Lindsay J. Meta-analysis of the effects of lifestyle modifications on coronary and carotid atherosclerotic burden. *Am J Cardiol* 2015;115:268–75.