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The impact of aerobic and isometric exercise on different measures of dysfunctional high-density lipoprotein in patients with hypertension

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Abstract

Background: Exercise training increases high-density lipoprotein (HDL) cholesterol, but its effect on HDL function is unclear. In hypertensives, exercise improves endothelial dysfunction, which is related to HDL function. In the present study, we assess for the first time the effects of different exercise modalities on two cell-free assays of HDL function.

Design: The study was conducted as a prospective randomized controlled trial in 75 hypertensive patients.

Methods: Patients were randomized in three groups: (a) handgrip isometric training five times weekly; (b) placebo-handgrip; and (c) aerobic exercise training at least three times per week. HDL function was assessed in serum samples at baseline and after 12 weeks of training by two independent assays that determine the proinflammatory phenotype (haptoglobin content) of a specific amount of HDL (Haptoglobin-HDL [HPHDL]) and oxidized HDL (HDLox) as a measure of reduced antioxidant function of HDL. HDL function measures were normalized by the measures of a pooled control of sera from healthy participants and by HDL-C levels (normalized ratio, no units).

Results: Aerobic exercise led to significant reduction of the HDLox from 0.99 ± 0.27 to 0.90 ± 0.29 (no units, $p = 0.03$). The HPHDL did not change in any training group. Changes of HDLox

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Author contributions

NP and TW contributed to the conception of the study, interpretation of data and drafted and revised the manuscript. SV, FB, FS and TK contributed to the acquisition and analysis of data. OR, IB and BS contributed to the analysis of data and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: the assay of HDLox is relevant to the patent PCT/US2015/018147.

correlated with reduction of the systolic blood pressure only after aerobic exercise ($R = 0.64$, $p = 0.03$).

Conclusions: Aerobic but not isometric exercise improves the antioxidant function of HDL in patients with hypertension. This improvement correlates positively with reductions of blood pressure.

Keywords

Aerobic exercise; isometric exercise; HDL function; lipids; hypertension

Introduction

High-density lipoprotein (HDL) particles have a broad spectrum of anti-atherogenic properties, including efflux of cellular cholesterol, vasodilation, reduction of apoptosis, antioxidant and anti-inflammatory effects.[1] However, HDL can lose its antiatherogenic properties in certain conditions like diabetes, chronic kidney disease and hypertension.[2] To date, there is no pharmacological approach to restore the beneficial properties of HDL. Identification of non-pharmacological strategies to improve HDL function is, therefore, clearly needed.

It is known that different types of exercise have different cardiovascular effects. For aerobic exercise, a clear scientific evidence for its positive effects on the reduction of blood pressure (BP), independent of the exercise intensity, exists.[3,4] The effect of isometric exercise on BP is controversial.[4] Exercise is also a potential intervention to increase HDL concentration (HDL-C)[4] and reduce triglycerides dependent on intensity and duration of the exercise program.[5] Previous cross-sectional studies assessed the association between dysfunctional HDL and exercise using a variety of HDL function assays and exercise protocols in different populations, leading to mixed results.[6,7] Some data indicate beneficial antioxidant and anti-inflammatory effects in patients with metabolic syndrome[8,9] and improvement of HDL mediated endothelial function after training programs in patients with heart failure.[10] Using a cell-free biochemical assay of HDL function, we have previously shown that chronic resistance training is associated with improved HDL redox activity (defined as reduced antioxidant activity and increased lipid peroxide content).[9]

In the present work, we evaluate for the first time the effects of exercise as a non-pharmacological intervention on HDL function in hypertension by using two independent cell-free assays.

Methods

Study population

In summary, 75 hypertensive subjects (either a BP of >140/90 mmHg or antihypertensive medication) were recruited at a German University Hospital (Charité – Universitaetsmedizin Berlin, Campus Benjamin Franklin). Epidemiological and clinical data of the study population have been published previously.[11] Regular intense engagement in physical exercise training (≥three sessions per week) in the past four weeks prior to inclusion in the

study, symptomatic peripheral arterial occlusive disease, aortic insufficiency or stenosis >stage I, hypertrophic obstructive cardiomyopathy, congestive heart failure (>NYHA II), uncontrolled cardiac arrhythmia with hemodynamic relevance, systolic office BP ≥180 mmHg, change of antihypertensive medication in the past four weeks prior to inclusion in the study and indication of unstable coronary artery disease were regarded as exclusion criteria. Written informed consent was obtained from all subjects. The study was approved by the local ethics committee at the Charité – Universitaetsmedizin Berlin.

Protocol

We performed a prospective, randomized, controlled study in a three-arm design comparing aerobic dynamic exercise with isometric handgrip training and ‘‘sham isometric handgrip training’’. The duration of the program was 12 weeks in each group. Patients randomized to aerobic exercise were encouraged to participate in endurance training for 30 min 3–5 times per week at moderate intensity according to levels 12–13 of the Borg scale of perceived exertion.[12] There was neither a structured exercise program nor a supervised program.

Isometric handgrip training was performed five times weekly. According to a standard protocol, each session contained two hand contractions of 2 min at 30% of maximal power with each arm. Sham-handgrip training was conducted based on the same protocol but with only 5% of maximal power. Based on previous trials, it was hypothesized that contractions with 5% of maximal power do not induce relevant cardiovascular effects. The Zona device was used in both groups (Zona Health Inc., Boise, USA). The standard commercial version aims at 30% of maximal power. The ‘‘sham devices’’ were developed by a software modification of the company. Participants were not informed whether they were randomized to handgrip or sham-handgrip training.

Blood sampling and BP measurements were performed at baseline and after 12 weeks. Antihypertensive medication was not allowed to be changed during the study period of 12 weeks.

Biomarker and laboratory assessment

Plasma lipid analysis.—Blood samples were stored and the lipid panel (total cholesterol, HDL-C and triglycerides) was measured in fasted ethylenediaminetetraacetic acid (EDTA)-plasma by standard validated clinical assays. low-density lipoprotein (LDL)-C was measured by a photometric method.

Oxidized HDL, (HDLox) oxidized LDL and Haptoglobin-HDL.—HDLox was quantified using a previously validated fluorometric biochemical assay that measures HDL lipid peroxidation based on the oxidation of the fluorochrome Amplex Red.[13]

Oxidized LDL was quantified using ELISA (Mercodia) according to manufacturer instructions.

Haptoglobin–HDL was determined by sandwich ELISA, as described previously.[14]

Study size calculation and statistical analysis.—As published previously, the study size was calculated by the expected effect of exercise on BP (reduction of about 7 mmHg of the systolic BP) resulting in the recruitment of 75 patients.[11] This sample size ($n = 75$) exceeded the necessary sample size ($n = 45$) to detect the expected effect on HDLox based on a standard deviation of 10%. Data were analyzed for normal distribution by the Kolmogorov–Smirnov test. Continuous parameters were normally distributed and were presented as mean ± standard deviation. Differences between the randomization groups were tested using one-way analysis of variance (ANOVA) for continuous parameters. A comparison of the categorical parameters was performed using the Pearson-x2-test. Changes in continuous parameters from baseline to follow-up were analyzed using paired two-tailed *t*-tests. Linear regression analysis was used to assess the association of HDLox with BP and cardiovascular risk parameters. $P < 0.05$ was regarded as statistically significant. All statistical analyses were performed using SPSS Statistics 19 (SPSS Inc, Chicago, IL, USA).

Results

Baseline variables

A total of 75 subjects with hypertension were randomized to aerobic exercise ($n = 25$), handgrip exercise ($n = 25$) and ‘‘sham-handgrip’’ ($n = 25$). A total of nine patients were excluded during the follow-up period due to changes in medication (violation of protocol, $n = 3$) or discontinuation of the training program ($n = 6$). Blood samples were successfully taken in 62 patients before and after the exercise program. For the final statistical analysis, data from 62 patients were used. Table 1 summarizes the epidemiological data, medication and the most frequent comorbidities.

Effect of exercise on lipids and HDL function

Aerobic exercise led to a significant reduction of the HDLox from 0.99 ± 0.27 to 0.90 ± 0.29 (no units, $p = 0.03$). No changes in the primary endpoint, HDLox, was seen in the handgrip and sham-handgrip group (Table 2). The HDL-associated haptoglobin (HPHDL), as another marker of dysfunctional HDL, did not change in any group after the training period (Figure 1).

Both aerobic and isometric exercise led to a significant reduction of the triglycerides from 199.4 ± 97.5 to 152.4 ± 59.4mg/dl and from 166.8 ± 88.2 to 130.9 ± 65.8 mg/dl accordingly ($p = 0.03$ each). The concentration of the HDL did not change during the 12 weeks training in any of the groups. In the aerobic group there was a numerically, but not significant, change from 37.6 ± 11.0 mg/dl to 40.5 ± 11.8 mg/dl ($p = 0.16$).

Association of HDL function with BP changes

Changes of the daytime systolic blood pressure (ΔBP) correlated significantly with changes of the HDLox (ΔHDLox) only in the aerobic group of patients. The same correlation was found for ΔHDLox and the daytime diastolic BP. A trend to a significant association was seen for changes of the 24 hours systolic and diastolic BP and HDLox after aerobic exercise. There were no significant associations between HDLox and BP values in any of the other groups (Table 3).

Association of HDL function to cardiovascular risk factors

We assessed the correlations of the HDLox and HPHDL to known cardiovascular parameters by performing a regression analysis of the whole population and by considering the baseline and follow-up measurements as single measurements (n = 124 values). There was a positive association between HDLox and body mass index (BMI), triglycerides and ambulatory BP (each $p< 0.05$, $R = 0.27–0.56$; Table 4 and Figure 2). No significant associations were seen between HPHDL and the several cardiovascular parameters (Table 4).

Discussion

The present study is the first randomized controlled trial that assessed the effects of aerobic and isometric exercise on the redox activity of HDL and on the haptoglobin content of HDL in hypertensive patients. Our findings show that aerobic exercise improved the antioxidant capacity of HDL (reduced HDLox). Haptoglobin HDL did not change with exercise. In contrast, neither isometric handgrip training nor the sham control training evoked any change in HDL function. The improvement of the functionality of HDL was evident independently of an increase of the plasma HDL and it correlated with improvement in daytime BP levels.

The novel results of our trial are important in several aspects. Firstly, the effect of exercise on HDL oxidation is one more piece in the puzzle in our understanding of the mechanisms underlying the cardiovascular benefits of exercise in hypertension. In the presence of hypertension, oxidative stress leads to endothelial dysfunction by different mechanisms such as nitric oxide (NO) inactivation, formation of peroxynitrite and endothelin expression stimulation.[15] Exercise can attenuate these deleterious effects of hypertension by improving the shear stress in endothelium and by reducing reactive oxygen species (ROS).[16] Some of these effects, like the stimulation of the endothelial cell NO production, are mediated by HDL.[17] We demonstrated that aerobic exercise was associated with improvement of both HDL function and BP. Future studies should explore the physiological impact of exercise on the cross-talk between endothelial function, BP and HDL function.[18]

Effects of exercise on HDL-C, HDLox and triglycerides

The hypothesis of a direct association of improvement of HDL function and BP is further supported by the fact that improvements of the antioxidative potential of HDL and BP in the present study occurred without any change in weight. In line with these results, we have previously shown that untrained young men have a higher proportion of dysfunctional HDL compared to strength-trained men irrespective of body weight status.[9] The absence of changes in total HDL-C and body weight in the present trial is not surprising. An increase of HDL-C requires high-intensity exercise training. Exercise training is associated with decreased plasma cholesteryl ester transfer protein activity.[19] A meta-analysis of the effects of aerobic exercise on lipid profiles in patients with cardiovascular disease showed a mean increase of 9% in HDL-C and a mean decrease of 10% in triglyceride concentrations.[20] In our study, participants were encouraged to engage in mild to moderate intensity exercise. Thus, improvements in HDL function may precede quantitative changes of HDL-C. Furthermore, the statin intake by about 50% of the patients prior to training may have

prevented further effects on lipids as demonstrated previously.[21] We found a significant decrease in triglycerides in both the aerobic and handgrip isometric group. A reduction of triglyceride concentrations has been already described for both aerobic and isometric exercise programs.[22]

Cell-free assays to assess HDL functionality

A cell-free assay that determines the lipid peroxide content of HDL (which is associated with reduced antioxidant HDL function) was used to assess the associations between oxidized HDL, hypertension and exercise. Most of the previous studies that assessed the effects of exercise on HDL function used the cholesterol efflux capacity and described inconclusive results.[8] Recently, Sarzynski et al.[23] demonstrated an improvement of some but not all of the used measures of HDL function via efflux capacity assessment. Other investigators have used other HDL subfractions like the HDL3, and demonstrated positive changes in response to exercise in diabetic but not in healthy subjects.[24] Tiainen et al.[25] showed an improvement of the antioxidative capacity in sedentary women after an exercise program of six months. In line with this, Iborra et al. showed an improvement of the HDL mediated antioxidant effects by measuring subfractions like HDL2 and HDL3 in patients with diabetes mellitus by demonstrating a decrease of plasma lipid peroxides.[6] However, no improvement of the activity of paraoxonase-1, an enzyme associated with the prevention of HDL oxidation,[26] was shown. This was achieved in the current trial by using an assay based on the Amplex Red to quantify the lipid peroxidation of HDL.[13] The current work is the first prospective trial assessing an intervention like aerobic training as a method to modify HDLox levels in patients with cardiovascular risk by using this cell-free assay. The cell-free assay constitutes a promising basis for a reliable readout to assess the antioxidative properties of HDL in clinical practice.[13]

No effect of exercise on HPHDL

We also assessed for the first time in a prospective trial the impact of exercise on another parameter of HDL function – HPHDL. HPHDL was not affected by any of the exercise protocols. The association of HPHDL with hypertension, until now, has not been well established. The HPHDL has been found to be increased in patients with coronary artery disease and diabetes mellitus, conditions associated with vascular inflammation.[27,28] Only few data exist on the effect of exercise on haptoglobin plasma levels. Haptoglobin may increase after acute exercise training in humans and after long-term exercise in mice.[29] The absence of any changes of the HPHDL in our population may express a low inflammation status in the absence of an established macrovascular disease or diabetes. Only two out of 62 patients of the current trial had diabetes and coronary artery disease. Another reason for the absence of any effects on HPHDL may be the program's duration of only 12 weeks. Further trials in patients with advanced cardiovascular diseases or with established cardiovascular risk factors are required to assess any effects of aerobic exercise on haptoglobin-HDL.

Strengths of the study

A strength of our study is the inclusion of different types of exercise to assess their effects on HDL function. We did not only assess the effects of aerobic exercise on HDL function but we compared it with another art of training, also expected to influence cardiovascular

metabolism by mechanisms other than changes of the oxidation status. To the best of our knowledge, no studies have investigated the effects of isometric exercise on HDL function before. Unlike aerobic exercise, the cardiovascular effects of isometric exercise may be primarily mediated by alterations in autonomic function.[30] The absence of any effects of isometric exercise on dysfunctional HDL supports the hypothesis that improvement of the oxidation status may be one of the underlying mechanisms for any effects of exercise on HDLox.

Limitations

The study is limited by its size. Like in real life, some patients stopped the aerobic exercise program, and the drop outs may have influenced the results. The lack of detailed information about the total frequency and duration of the aerobic exercise limits interpretations about the effect-size of different levels of exercise intensity of HDL. Furthermore, the lack of a clinical measurement of the endothelial function did not allow us to fully determine the impact of aerobic exercise on the cross-talk between endothelial function, HDL function, BP and exercise. It can be only assumed that changes in oxidation status and endothelial function led to improvement of the HDLox.

Conclusion and future directions

In conclusion, we demonstrate a direct beneficial effect of aerobic exercise on dysfunctional HDL in patients with hypertension. This novel finding constitutes one more step in our understanding of the exercise-induced cardiovascular benefits and thereby supports current hypertension guidelines recommending aerobic exercise on a regular basis. Moreover, these data show that the effects of lifestyle interventions on HDL function can be assessed by a cell-free assay. These data are encouraging for the potential implementation of HDL quality assays in daily clinical practice. The search for mechanisms underlying the cardiovascular benefits of physical activity will have to continue.

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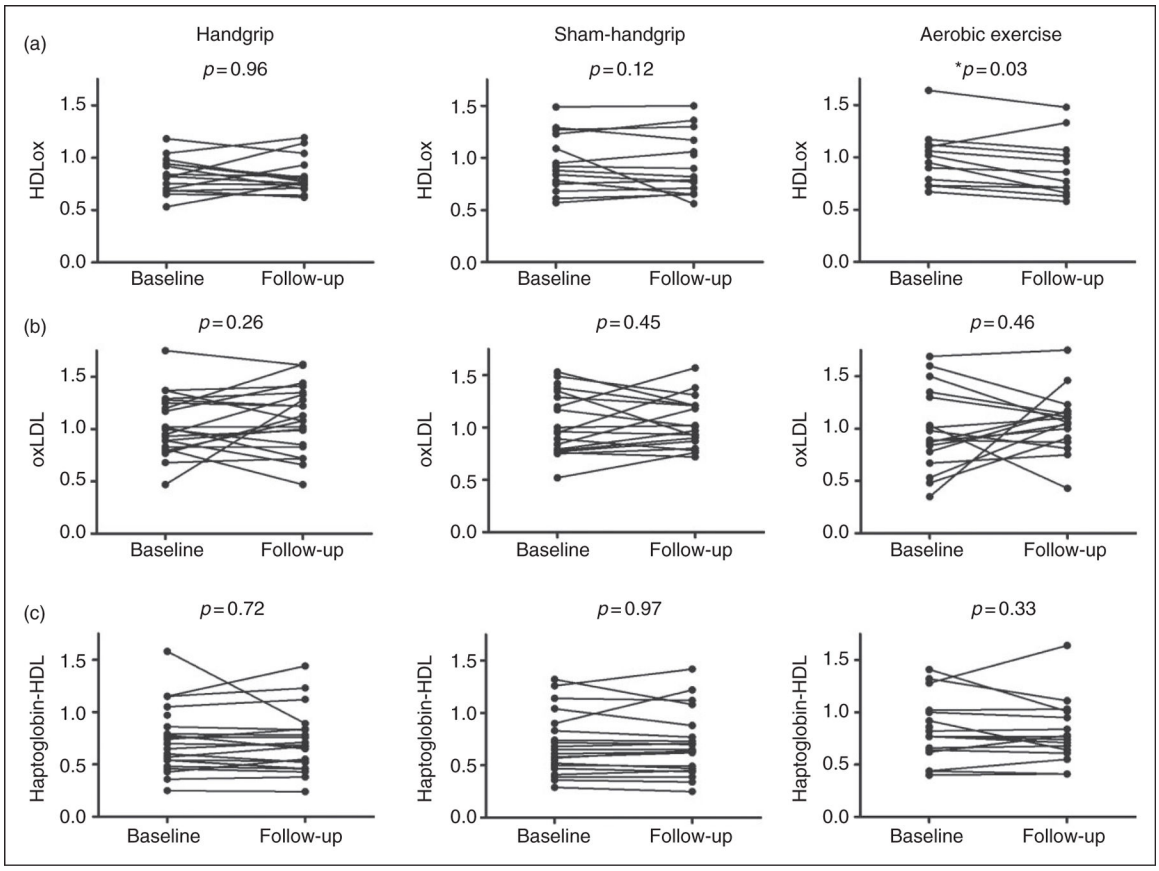

Figure 1.

Effects of isometric handgrip training, sham-handgrip training and aerobic exercise on (a) oxidized HDL (HDLox), (b) oxidized LDL (oxLDL) and (c) haptoglobin-bound HDL. *$p <$ 0.05 regarded as significant.

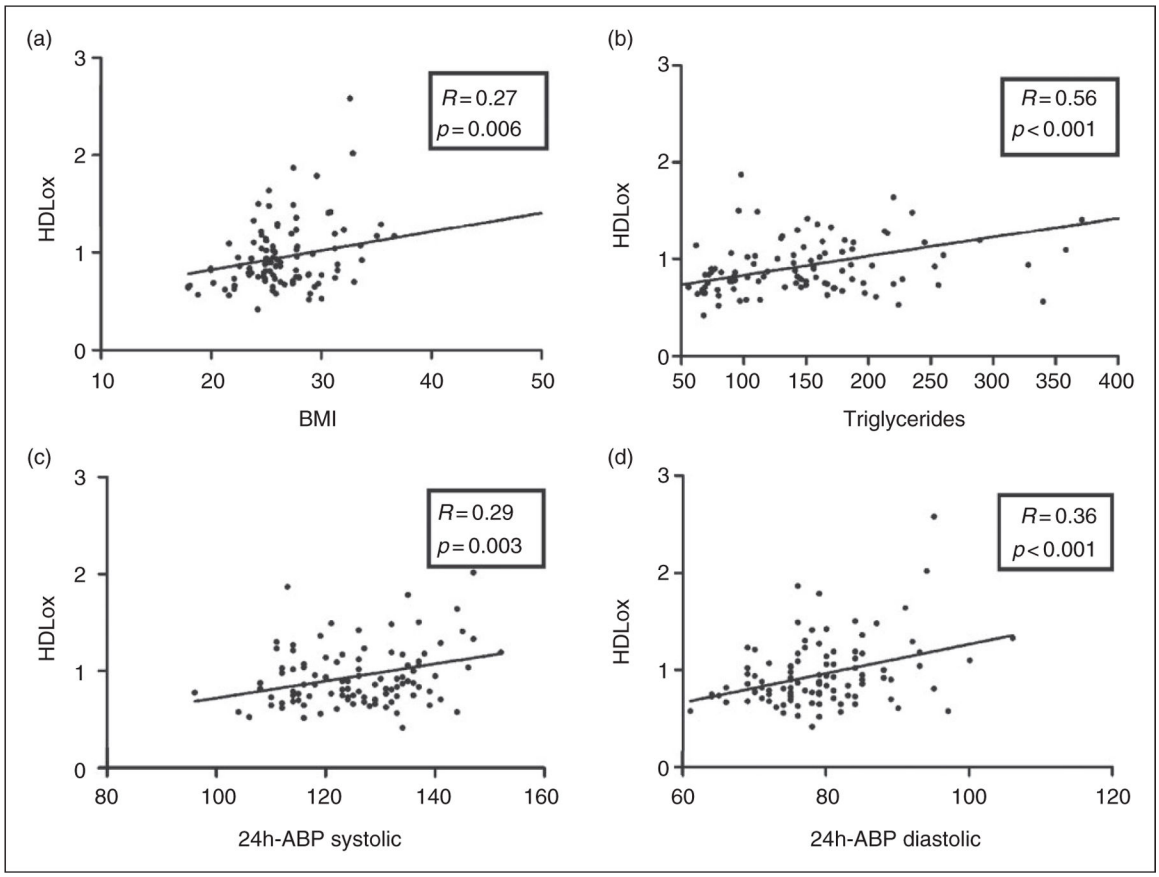

Figure 2.

Regression analysis of oxidized HDL (HDLox) with other cardiovascular risk factors in the overall study population: (a) body mass index (BMI); (b) triglycerides; (c) 24h ambulatory systolic blood pressure; (d) 24 h ambulatory diastolic blood pressure.

Table 1.

Demographic data of the study population.

Study population	Handgrip (*n* = 23)	Sham-handgrip (*n* = 21)	Aerobic exercise (*n* = 18)	p
Female	16 (69.6%)	11 (52.4%)	9 (50.0%)	0.37
Age (years)	59.8±10.5 (41–75)	61.5±7.5 (49–76)	61.6±11.3 (43–75)	0.80
Caucasian ethnicity	23 (100%)	21 (100%)	18 (100%)	1.0
Body mass index (kg/m^2)	26.2±3.9	28.3±7.1	26.9±3.5	0.39
Antihypertensive therapy	18 (78.3%)	16 (76.2%)	15 (83.3%)	0.86
ACE inhibitor or ARB	13 (56%)	10 (48%)	12 (67%)	0.32
Diuretic	5 (21%)	5 (24%)	4 (22%)	0.92
Calcium channel blocker	4 (17%)	6 (29%)	3 (17%)	0.21
Beta-blocker	5 (22%)	7 (33%)	4 (22%)	0.64
Other	0	1 (5%)	0	0.39
Statin	7 (30.4%)	12 (57.1%)	9 (50.0%)	0.18
Sedentary lifestyle (no regular exercise training)	9 (39.1%)	11 (52.4%)	8 (44.4%)	0.37
Smoking	6 (26%)	6 (24%)	3 (17%)	0.29
Concomitant diseases				
Diabetes mellitus	0 (0.0%)	2 (9.5%)	0 (0%)	0.13
Atrial fibrillation	1 (4.3%)	3 (14.3%)	2 (11.1%)	0.52
Coronary heart disease	0 (0.0%)	2 (9.5%)	0 (0%)	0.13

ANOVA test was performed for differences among the study groups.

ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 2.

Effects of aerobic exercise, isometric handgrip training and sham handgrip training on BMI, routine lipid profile and measurements of lipid function.

	Handgrip isometric (*n* = 23)			**Sham-handgrip isometric (*n* = 21)**			**Aerobic exercise (*n* = 18)**		
	Baseline	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***
BMI (kg/m^2)	26.2±3.9	26.2±3.7	0.32	28.3±7.1	28.2±7.3	0.57	26.9±3.5	26.7±3.5	0.12
HDL (mg/dl)	44.9±9.1	44.9±9.5	0.98	39.9±13.5	40.7±13.4	0.73	37.6±11.0	40.5±11.8	0.16
LDL (mg/dl)	124.8±43.7	118.5±36.0	0.47	112.5±39.6	126.3±47.9	0.06	124.6±56.4	130.6±40.3	0.63
Cholesterol (mg/dl)	235.4±64.6	211.9±51.1	0.06	211.8±54.7	209.0±53.2	0.61	226.3±67.1	219.6±45.5	0.74
Triglycerides (mg/dl)	166.8±88.2	130.9±65.8	0.03	174.5±113.9	166.5±120.4	0.41	199.4±97.5	152.4±59.4	0.03
HDLox (no unit)	0.83±0.17	0.83±0.17	0.96	1.11±0.52	1.0±0.39	0.12	0.99±0.27	0.90±0.29	0.03
HPHDL (no unit)	0.90±0.70	0.87±0.65	0.55	0.70±0.30	0.70±0.31	0.96	0.93±0.52	0.89±0.44	0.31
Oxidized LDL (no unit)	1.07±0.32	1.14±0.36	0.26	1.09±0.35	1.12±0.33	0.57	0.98±0.39	1.06±0.29	0.45

HDLox: oxidized high-density lipoprotein normalized for HDL concentration; HPHDL: haptoglobin bound to HDL normalised for haptoglobin; oxidized LDL: oxidized LDL adjusted for LDL concentration.

Paired *t*-tests between baseline and follow-up. p<0.05 (bold) regarded as significant.

Table 3.

Correlations of changes of the HDLox (ΔHDLox) to changes of the ambulatory blood pressure from baseline to follow-up within the groups.

	Handgrip isometric (*n* = 23)		**Sham-handgrip isometric (*n* = 21)**		**Aerobic exercise (*n* = 18)**	
	R	**p**	**R**	**p**	**R**	**p**
Δsys 24 h ABP (mmHg)	0.02	0.94	−0.01	0.98	0.53	0.08
Δdias 24 h ABP (mmHg)	−0.26	0.34	0.09	0.74	0.52	0.08
Δdaytime systolic ABP (mmHg)	−0.03	0.92	−0.08	0.76	0.64	0.03
Δdaytime diastolic ABP (mmHg)	−0.27	0.33	0.04	0.89	0.60	0.04
Δnighttime systolic ABP (mmHg)	−0.16	0.56	0.03	0.92	0.15	0.65
Δnighttime diastolic ABP (mmHg)	−0.28	0.31	0.13	0.63	0.14	0.67

ΔABP: changes of the ambulatory blood pressure from baseline to follow-up; Δdias: changes of diastolic blood pressure; Δ HDLox: changes of oxidized high-density lipoprotein normalized for HDL concentration; Δsys: changes of systolic blood pressure.

Bivariate Pearson correlation analyses. p<0.05 (bold) regarded as significant.

Table 4.

HDLox and HPHDL correlations with indices of vascular and metabolic health.

	HDLox		HPHDL	
Outcome	***R***	***p***	***R***	***p***
Age	−0.04	0.68	0.02	0.79
BMI	0.27	0.006	0.04	0.66
Total cholesterol	−0.06	0.54	0.09	0.3
Triglycerides	0.56	<0.001	−0.002	0.98
HDL	−0.81	<0.001	−0.17	0.08
LDL	0.06	0.53	−0.05	0.59
Oxidized LDL	0.09	0.37	−0.09	0.33
HPHDL	−0.14	0.16	−	−
24 h sys. BP	0.29	0.003	−0.01	0.89
24 h diast. BP	0.36	<0.001	0.17	0.06

24h diast. BP: 24h ambulatory diastolic blood pressure; 24h sys. BP: 24h ambulatory systolic blood pressure; HDLox: oxidized high-density lipoprotein normalized for HDL concentration; HPHDL: haptoglobin bound to HDL normalized for haptoglobin.

Pearson correlation analysis. p<0.05 (bold) regarded as significant.