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ORIGINAL ARTICLE

The effects of resistance training on ApoB/ApoA-I ratio, Lp(a) and inflammatory markers in patients with type 2 diabetes

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Abstract The purpose of this study was to investigate the effects of resistance training (RT) on novel cardiovascular risk factors in patients with type 2 diabetes mellitus (T2DM). We enrolled 52 overweight/obese, type 2 diabetic patients, with inadequate glycemic control (HbA1c > 6.5 %), but without overt diabetic vascular complications. Participants were randomly assigned into two equivalent groups ($n = 26$): (1) Resistance exercise group: subjects underwent a supervised RT program (3-times/week, 60 min/session, 2–3 sets of 8 machine-weight exercises, 60–80 % of one-repetition maximum). (2) Control group (CG): at study entrance, they received a structured exercise counseling to increase daily physical activity. Clinical parameters, cardiorespiratory capacity, glycemic and lipid profile, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), Lipoprotein(a) [Lp(a)], insulin resistance (HOMA-IR), high-sensitivity CRP (hsCRP), fibrinogen were measured before and after 3 months. RT significantly reduced glycemic indexes, insulin resistance and systolic blood pressure, compared to CG ($p < 0.05$). Moreover, exercise-treated patients conferred a remarkable downregulation in ApoB levels (from 135.92 ± 30.97 mg/dL to 85.9 ± 26.46 mg/dL, $p < 0.001$) as compared to CG (from 126.33 ± 36.59 mg/dL to 116.23 ± 27.52 mg/dL, $p = 0.872$) ($p < 0.001$). Similarly, ApoB/ApoA-I ratio was considerably decreased in REG rather than CG (-0.32 ± 0.09 vs 0.02 ± 0.01, $p < 0.001$). Notably, ApoA-I, Lp(a), hsCRP, fibrinogen, the rest of lipid parameters, body weight and exercise capacity remained unaltered in both groups ($p > 0.05$). Among variables, HOMA-IR reduction was found to be an independent predictor of changes in ApoB/ApoA-I ratio ($R^2 = 0.406$, $p = 0.041$) in REG. Long-term RT ameliorated glycemic control, insulin sensitivity and ApoB/ApoA-I ratio in individuals with T2DM. Although we did not observe significant benefits in the rest of cardiovascular risk factors, our results indicate a merely beneficial impact of RT.

Keywords Type 2 diabetes · Resistance training · Exercise · Insulin resistance · Apolipoprotein A-I · Apolipoprotein B · Lp(a) · hsCRP

Introduction

Chronic exercise along with standard care has been advocated as treatment for type 2 diabetes mellitus (T2DM) worldwide [1]. Numerous studies of structured exercise or even self-reported physical activity interventions have consistently reported improvements in traditional (e.g., lipids, insulin resistance, hypertension) [2, 3] and "pleiotropic", non-traditional cardiovascular risk factors in T2DM [4, 5].

Among exercise modalities, resistance training (RT) of even low-intensity has shown beneficial influence on body composition, as expressed by muscle- and fat-mass, in diabetic patients [6, 7]. Moreover, initial data suggested that long-term RT may improve glucose tolerance and insulin sensitivity in patients with T2DM [8]. However, a

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recent meta-analysis documented a wide heterogeneity in the metabolic consequences of RT alone or combined with other forms of exercise, outlining the absence of significant impact on most cardiovascular markers, like inflammatory markers [9]. Thus, further studies are required in order to clarify the metabolic and cardiovascular effects of RT.

It is well-documented that total cholesterol, low-density cholesterol (LDL-C), apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB) exert high-predictive value in major cardiovascular events in the general population [10]. Notably, LDL-C levels are not always a good or adequate indicator of cardiovascular risk. The ApoB/ApoA-I ratio seems to be a better indicator of cardiovascular disease (CVD) risk in patients with T2DM than LDL-C [11]. The latter ratio provides a representative therapeutic target in the diabetic population. In parallel, Lipoprotein(a) [Lp(a)], a subtype of LDL-C that carries Apo(a), is part of a plasminogen family with potentially atherogenic and thrombotic properties predisposing to coronary artery disease (CAD) [12]. Despite the clinical importance of the above lipoproteins, the impact of exercise training, especially the RT, on their plasma levels is still obscure in T2DM.

In the current study, we assessed the effects of RT on metabolic parameters and circulating levels of novel cardiovascular risk factors, like ApoA-I, ApoB, Lp(a), high-sensitivity C-reactive protein (hsCRP) and fibrinogen, in men and women with T2DM. We also examined the exercise-induced changes in ApoB/ApoA-I ratio across the changes of other variables.

Research design and methods

Subjects—study design

The present study enrolled 52 patients with T2DM, mean age 61.3 ± 2.1 years old, already treated with oral anti-diabetic medications, but without adequate glycemic control (HbA1c > 6.5 %). Patients were also considered eligible only if they were overweight/obese (BMI > 25 kg/m^2), with diabetes duration >1 year. Exclusion criteria included: CAD or overt cardiac-origin symptoms, diabetic micro-vascular complications, insulin treatment, autoimmune diseases, untreated hypothyroidism, osteoporosis, liver impairment (ALT > 2.5 times higher than the upper normal limit), renal insufficiency (creatinine levels >2.0 mg/dL), atrial fibrillation, malignancy, and orthopedic problems limiting physical activity.

Only the statistician of our team had access to the database until the randomization was actually done. We used a computer-generated randomization list stratified by gender in blocks of four to ensure close balance of the numbers in each group. Therefore, all participants were randomly assigned into two equivalent groups ($n = 26$) for 3 months.

Resistance exercise group (REG, n = 26)

Subjects underwent a structured, supervised program of RT, described in the next section.

Control group (CG, n = 26)

At study entrance, control subjects received a structured exercise counseling to increase daily physical activity. The aim was each individual to accumulate 150 min per week of self-reported, leisure-time, physical activity (e.g. walking briskly, cycling outdoor, swimming with moderate effort, etc.) varying from low to high-intensity. Patients were asked to record in personal diaries the duration, the type and the self-estimated intensity of their activities weekly. Diaries were checked by an exercise physiologist at a meeting, once every month. Then, patients were further encouraged to achieve and/or maintain exercise targets.

At baseline and after 3 months, all co-morbidities, medications, and smoking habits were recorded using structured questionnaires. At the same time intervals, cardiorespiratory capacity (assessed on ergocycle), blood samples, body mass index (BMI), waist–hip ratio (WHR) and blood pressure (BP) were obtained. Patients were asked to maintain unaltered pharmacological treatment and dietary habits throughout the study, unless it was deemed medically necessary. Constructed recommendations for smoking cessation were provided to all smokers at baseline.

The study was approved by the local ethics committee and it was conducted in accordance with the Declaration of Helsinki. All participants provided a written informed consent before enrolment.

Exercise training protocol

In resistance-trained patients, workouts were performed three times a week in group-structured, supervised sessions. The duration of each session was initially set at 45 min and gradually progressed to 60 min including 10 min of calisthenics (ball games, jumping, rope skipping and gymnastics) before and after RT sets. Each patient performed two to three sets of eight major exercises using machine weights (Cybex International, Medway, MA, USA). The exercise training program targeted at all major muscle groups of the body including: seated leg press, knee extension, knee flexion, chest press, lat pulldown, overhead press, biceps curl, and triceps extension. Approximately, 1 min of rest was provided between exercises and 3 min between sets.

Prior to starting the exercise training, subjects underwent a graded preliminary test of each type of exercise to determine the one-repetition maximum (1-RM—maximum load achieved in one repetition). Based on the latter results, the intensity of exercises was individualized and these sets were performed with moderate (60–80 % of 1-RM) load involving moderate volume of exercise (6–8 repetitions/exercise). 1-RM was adapted within the first 4 weeks of training, where it was maintained for the remainder of the study. Compliance to training was defined as the number of training sessions attended divided by the number offered multiplied by 100 %. Compliance less than 80 % was considered inadequate and patients were excluded from analysis.

Body composition assessment

BMI was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was assessed at the level midway between the lower rib margin and the iliac crest. The hips were measured at the level of the greater femoral trochanters. Thus, WHR expressed waist circumference divided by hip girth. BP was measured twice, after keeping all participants in a sitting position for 15 min. There was a 5 min interval between the two measurements and the mean value was estimated for study purposes. The percentage of fat-mass was calculated using a body composition analyzer (Bodystat 1500, Bodystat Ltd, Isle of Man, British Isles), which is based on bio-electrical impedance assessment.

Cardiorespiratory capacity assessment

We assessed cardiorespiratory capacity of all participants at baseline and at the end of the study using an electronically braked ergocycle. The workload was initially set at 25 W, for 2 min, and thereafter was increased by 25 W every 2 min until patients were unable to either continue or retain a constant rate of pedal revolutions. Oxygen uptake and carbon dioxide output were measured continuously by a gas exchange analyzer (COSMED K4, Rome, Italy) using facemask and breath-by-breath technique. Peak oxygen consumption (VO2peak) achievement was considered by one of the following criteria: (1) Respiratory exchange ratio > 1.1, (2) heart rate within 10 beats/min of the age-predicted maximal heart rate and (3) no significant increase of VO_2 (<1 ml/kg/min) despite the increase of work rate. There was continuous electrocardiographic recording during the test and the whole procedure was closely supervised by an experienced physician. The heart rate response to the aforementioned test was used to prescribe exercise training program. A prior familiarization ergospirometry testing of short-duration and constant, low-intensity was performed one week before study beginning. All assessments were performed at least 48 h after the last exercise session, in order to assess the true training effects.

Blood analyses

At baseline and at the end of the study, blood samples were obtained between 8.00 and 10.00 a.m. after an overnight fast. Patients were instructed to refrain from any intensive physical activity for at least 48 h before all measurements. Lipid and fasting plasma glucose (FPG) were enzymatically measured (Roche/Hitachi 912 analyzer; Roche Diagnostics, Switzerland). LDL-cholesterol was calculated from the Friedewald equation. Measurement of HbA_{1c} was made by high-performance liquid chromatography (Menarini Diagnostics, Italy). Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) [13]. ApoA-I, ApoB and Lp(a) concentrations were determined by immunonephelometry (Olympus AU640, Medicon, Watford, UK). Nephelometric assay (Dade Behrin, BNII, Marburg, Germany) was used for high-sensitivity C-reactive protein (hsCRP) determination. Fibrinogen was measured by the Clauss method twice and the mean value was used for study purposes. Samples were frozen and stored (−80 °C) until analysis for apolipoproteins, Lp(a) and hsCRP in the same assay.

Statistical analysis

Normality of distribution was assessed by Shapiro–Wilk test. Concerning the normal distribution of all continuous variables comparison between groups of baseline, final values and changes of variables was performed by Student's t test. Changes over time within groups were analyzed by paired samples t test. For missing values handling, we excluded patients with incomplete data. Chi-square test was performed for comparison of categorical data between groups. Pearson correlation and standard multiple regression analysis quantified the relationship between changes of variables and their independent predictors, respectively. For all calculations we used SPSS 16.0 (SPSS Inc, Chicago, USA). A two-tailed p value < 0.05 was considered as statistically significant.

Results

Clinical and biochemical variables are listed in Tables 1,2 and Fig. 1. All groups did not differ at baseline. Five patients discontinued the study. Two patients stopped

Table 1 Baseline characteristics of participants who completed the study

	Resistance exercise group ($n = 23$)	Control group ($n = 24$)	p
Gender (men/women)	7/16	5/19	0.412
Age (y)	61.5 ± 5.4	64.6 ± 4.3	0.307
Diabetes duration (y)	6 ± 2.8	5.6 ± 1.9	0.897
Smokers (*n*)	6 (26.1 %)	7 (29.2 %)	0.766
Anti-hypertensive medications (*n*)	20 (90 %)	19 (79.17 %)	0.291
Statins (*n*)	14 (60.9 %)	13 (54.2 %)	0.786
Anti-diabetic regimen (*n*)			
Sulfonylurea	2	2	
Metformin	4	6	
Sulfonylurea + metformin	12	10	
DPP4 inhibitors + metformin	5	6	
hsCRP (mg/L)	3.8 ± 1.34	3.66 ± 0.87	0.811
Lp(a) (mg/dL)	9.33 ± 2.33	10.22 ± 3.15	0.661
ApoA-I (mg/dL)	196.5 ± 32.51	191.79 ± 64.36	0.814
ApoB (mg/dL)	135.92 ± 30.07	126.33 ± 36.59	0.439
ApoB/ApoA-I ratio	0.72 ± 0.23	0.72 ± 0.28	0.982

Data are mean ± SD

y years, *n* number of patients, *DPP*4 dipeptidyl-peptidase 4, *hsCRP* high-sensitivity CRP, *Lp*(*a*) *Lipoprotein*(*a*), *ApoA-I* Apolipoprotein A-I, *ApoB* Apolipoprotein B

Table 2 Baseline and end-values of variables in both groups

	Resistance exercise group ($n = 23$)			Control group ($n = 24$)			
	Baseline	3 months	*P1*	Baseline	3 months	*P1*	*P2*
BMI (kg/m^2)	32.74 ± 4.05	32.71 ± 3.2	0.943	31.58 ± 5.71	31.71 ± 6.19	0.610	0.554
WHR	0.992 ± 0.099	0.981 ± 0.088	0.452	0.956 ± 0.103	0.967 ± 0.129	0.280	0.115
Fat-mass (%)	36.5 ± 8.1	36.4 ± 8.8	0.947	34.2 ± 6.9	34.5 ± 8.2	0.956	0.831
Systolic BP (mmHg)	121 ± 9	111 ± 9	0.042	144 ± 16	139 ± 19	0.416	0.030
Diastolic BP (mmHg)	71 ± 9	66 ± 5	0.087	83 ± 11	81 ± 9	0.715	0.061
HbA1c (%)	7.4 ± 0.4	7.1 ± 0.6	0.043	7.5 ± 0.5	7.7 ± 0.6	0.252	0.020
FPG (mg/dL)	169 ± 27	147 ± 27	0.009	175 ± 28	182 ± 36	0.466	<0.001
TChol (mg/dL)	238 ± 24	222 ± 17	0.317	239 ± 49	241 ± 55	0.981	0.291
HDL-C (mg/dL)	51 ± 15	50 ± 12	0.847	52 ± 12	51 ± 13	0.793	0.885
LDL-C (mg/dL)	155 ± 26	145 ± 17	0.146	148 ± 51	143 ± 40	0.899	0.488
TG (mg/dL)	159 ± 60	135 ± 68	0.087	195 ± 52	205 ± 72	0.505	0.066
Insulin (mU/L)	9.52 ± 4.22	7.7 ± 1.23	0.034	10.24 ± 4.91	10.29 ± 5.89	0.553	0.003
HOMA-IR	3.97 ± 1.86	2.79 ± 0.48	0.014	4.42 ± 1.01	4.62 ± 1.47	0.669	<0.001
Fibrinogen (mg/dL)	369.01 ± 67.32	340.12 ± 52.31	0.238	353.22 ± 61.77	362.33 ± 68.76	0.886	0.188
WBC (cells/μL)	7125 ± 2600	6875 ± 1043	0.307	6690 ± 1233	6799 ± 1409	0.615	0.181
VO_{2peak} (mL/kg/ min)	24.18 ± 2.78	24.40 ± 4.31	0.764	24.42 ± 5.5	24.18 ± 5.57	0.582	0.395

Data are mean ± SD

BMI body mass index, *WHR* waist–hip ratio, *BP* blood pressure, *FPG* fasting plasma glucose, *TChol* total cholesterol, *TG* triglycerides, *HOMA-IR* homeostasis model assessment-insulin resistance, *WBC* white blood cells, *P1* *p* values of changes of variables within groups, *P2* *p* values of changes of variables between groups

training due to time constraints, one patient declined repeated measurements and two patients were not found for follow-up. Thus, 23 patients in REG and 24 in CG were eligible for analysis. All exercise-treated patients showed high compliance to structure exercise (attendance 91 ± 4 % of exercise sessions). On the other hand, only 45.8 % of controls achieved the target of exercise >150 min/week. The concomitant medications were similar among groups and remained unaltered throughout the study. No adverse events were referred in both groups.

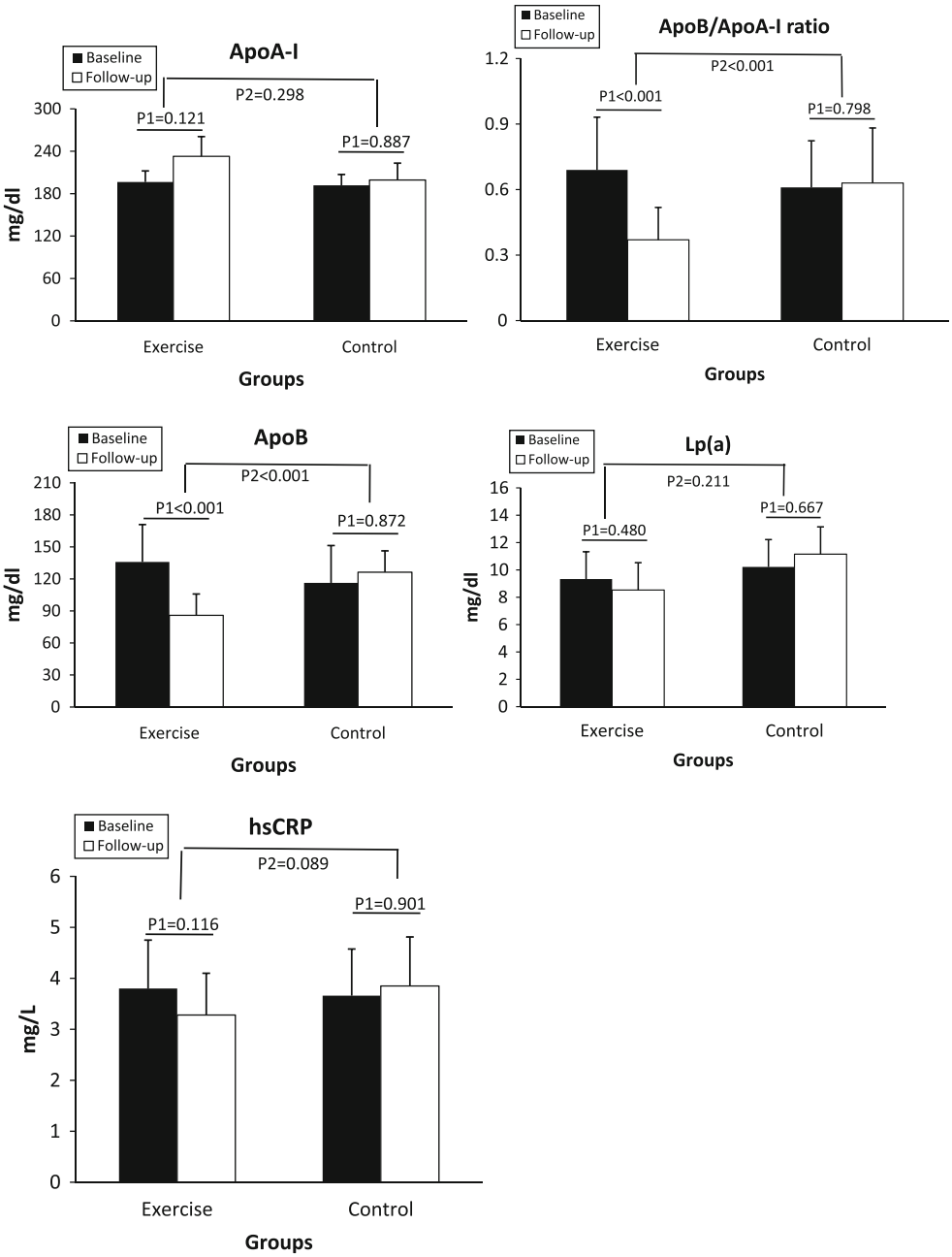

Fig. 1 Effects of 3-months resistance training on ApoA-I, ApoB, ApoB/ApoA-I ratio, Lp(a), and hsCRP concentrations. *P1*, *p* values of changes of variables within groups; *P2*, *p* values of changes of variables between groups

Glycemic control, insulin resistance and exercise capacity and body composition

After the completion of the study a significant decrease in FPG ($p < 0.001$) and HbA1c ($p = 0.020$) was observed in the REG compared to CG. That effect was accompanied with significant improvement in insulin sensitivity as expressed by the lower insulin ($p = 0.003$) and HOMA-IR ($p < 0.001$) levels in the REG (Table 2).

As expected, RT did not confer any significant change in the cardiorespiratory capacity of the exercise-treated patients compared to baseline ($p = 0.764$) and control diabetic patients ($p = 0.395$). Notably, RT did not significantly alter BMI, WHR, and percentage of fat-mass in our diabetic population ($p > 0.05$) (Table 2).

Blood pressure, lipid profile and cardiovascular risk factors

As presented in Table 2, RT significantly reduced systolic BP ($p = 0.030$) and tended to decrease diastolic BP ($p = 0.061$) and triglycerides ($p = 0.081$) levels compared to CG. On the other hand, we did not find significant changes in total cholesterol, HDL and LDL-C values within and between groups ($p > 0.05$).

As shown in Fig. 1, RT treatment resulted in a significant decrease in ApoB concentration (from 135.92 ± 30.97 mg/dL to 85.9 ± 26.46 mg/dL, $p < 0.001$) as compared to its reduction in CG (from 126.33 ± 36.59 mg/dL to 116.23 ± 27.52 mg/dL, $p = 0.872$) ($p < 0.001$). Similarly, the ApoB/ApoA-I ratio was considerably decreased in REG (from 0.69 ± 0.18 to 0.37 ± 0.10) rather than CG (from 0.61 ± 0.19 to 0.63 ± 0.12) ($p < 0.001$). Finally, between groups comparison showed a non-significant reduction in inflammatory markers as well as in hsCRP (ΔhsCRP REG: −0.52 ± 0.26 mg/L vs CG: 0.19 ± 0.06 mg/L, $p = 0.189$), white blood cells count (ΔWBC in REG: 250 ± 56 cells/μL vs CG: 109 ± 22 cells/μL, $p = 0.181$) and fibrinogen (Δfibrinogen in REG: −28.89 ± 12.34 mg/L vs CG: 9.11 ± 3.66 mg/L, $p = 0.188$). No significant change was detected in Lp(a) concentrations within and between groups (REG: from 9.33 ± 2.33 mg/dL to 8.53 ± 1.87 mg/dL and CG: from 10.22 ± 3.15 mg/dL to 11.15 ± 3.59 mg/dL) ($p > 0.05$).

Correlations

We next examined the significant changes of ApoB/ApoA-I ratio in relation to the changes of the other variables within REG. The exercise-induced reduction in ApoB/ApoA-I ratio correlated with HbA1c ($r = 0.294$, $p = 0.024$), and HOMA-IR ($r = 0.601$, $p = 0.025$) reduction. The above variables with entered standard multiple regression analysis, which revealed HOMA-IR changes as independent determinant of ApoB/ApoA-I ratio reduction in REG ($R^2 = 0.406$, $p = 0.041$).

Discussion

The main finding of this study is that RT may alleviate hyperglycemia, insulin resistance, atherogenic dyslipidemia, as expressed by ApoB/ApoA-I ratio, and decrease systolic blood pressure in overweight/obese individuals with T2DM. The aforementioned exercise-induced reduction in ApoB/ApoA-I ratio was independently associated with HOMA-IR reduction in our diabetic population. On the other hand, RT did not significantly influence Lp(a), inflammatory mediators, and body composition in patients with T2DM.

The American Heart Association and the American Diabetes Association have incorporated exercise training as the cornerstone of T2DM management [1]. In our study, RT significantly improved glycemic profile, despite the lack of weight-loss, which is of clinical relevance. Most, but not all, previous studies have shown a modestly significant improvement in glycemic regulation in diabetic patients undergoing RT [2, 14]. Dunstan et al. (2002) proposed moderate weight-loss induced by high-intensity RT as a prerequisite for effective glucose-lowering in diabetic patients [15]. Nevertheless, modest glucose homeostasis improvement has been also observed even without weight-loss [2]. In HART-D trial, RT failed to significantly reduce HbA1c levels in type 2 diabetic patients [16]. There are several points which may explain the differences between our intervention and HART-D trial. Compared with our participants, HART-D trial patients performed a RT program of lower volume (140 min/week, 50–80 % of maximum oxygen consumption), had a high prevalence of non-white participants (47 %), and there was an important portion of insulin-treated patients, whereas insulin usage was an exclusion criterion in our study.

In parallel, our results confirmed the suppression of insulin resistance in patients undergoing RT program [17]. One possible explanation of the positive effects of RT on insulin resistance may derive from the increased number of glucose transporter-4 (GLUT4) proteins. In skeletal muscle cells, GLUT4 is thought to be responsible for insulin- and contraction-stimulated glucose transport in skeletal muscle [18]. In addition, increasing total muscle-mass will ultimately result in an increase in total insulin-mediated glucose uptake. Another possible underlying mechanism for improved glucose uptake could be an increased number of insulin receptors in the muscle cell.

In parallel, accumulated randomized control trials indicated the favorable alterations in HbA1c and systolic blood pressure in patients with abnormal glucose regulation [19, 20]. In agreement to previous reports, we documented a significant decrease in systolic BP after RT, despite the absence of changes in exercise capacity. That effect could be ascribed to insulin resistance alleviation and it is of clinical importance. On the other hand, our RT program conferred significant changes neither in body weight nor in body composition. Perhaps, a higher intensity program would have resulted in a significant improvement of body homeostasis.

ApoB is essential for the binding of LDL-C particles, allowing cells to internalize LDL-C and thus absorb cholesterol. An excess of ApoB-containing particles highly correlates with the level of non-HDL-C cholesterol [21] and it is a main trigger in the atherogenic process [22]. On the other hand, levels of ApoA-I strongly correlate with those of HDL-C, and expression of ApoA-I may be largely responsible for determining the plasma level of HDL-C, protecting against CVD. Notably, the calculated ApoB/ApoA-I ratio has been consistently reported as a prognostic cardiovascular risk factor superior than LDL-C [23]. To our knowledge, this is the first study demonstrating the favorable impact of RT on ApoB levels and ApoB/ApoA-I ratio in the diabetic population. Two previous studies in

T2DM had also reported similar results after supervised aerobic exercise training [24, 25]. In those studies, aerobic exercise had additionally increased ApoA-I levels, leading to a further suppression of ApoB/ApoA-I ratio. The latter effect in our study was exclusively attributed to ApoB reduction. Concerning the close relationship of upregulated ApoB/ApoA-I ratio with cardiac events, our striking finding implicates a CVD protection. Looking for the underlying mechanisms, we found an independent, positive association of ApoB/ApoA-I ratio lowering, after RT treatment, with the insulin resistance reduction. In other words, RT seemed adequately effective to promote insulin sensitivity and a more favorable lipid profile. The latter effect has been also proved in the large-scale, randomized DARE trial, where RT alone or combined with aerobic training reduced cholesterol in remnant-like lipoprotein particles, an independent risk factor of CAD [7]. Whether those changes contribute to clinical outcomes remains to be proved in the long-term.

Epidemiological and experimental studies provide overwhelming evidence that Lp(a) may promote atherogenesis and thrombosis via its LDL-like and plasminogen-like mechanisms [11]. A single study has previously demonstrated a significant reduction of Lp(a) levels in both type 1 and type 2 diabetic patients after a supervised 3-month physical exercise program [26]. However, that effect was limited only in the diabetic subgroup with excessively upregulated Lp(a) levels at baseline (>300 mg/L) and not in the whole study-cohort. Furthermore, there is an inverse relationship of cardiorespiratory fitness with Lp(a) levels in patients with T2DM [27]. Our RT program did not succeed to change Lp(a) levels, perhaps due to the lower baseline levels of Lp(a) and the lack of changes in the cardiorespiratory fitness. However, in other previous studies serum Lp(a) levels did not change in response to moderate-intensity, long-term exercise interventions, despite improvements in fitness level and other lipoprotein levels in the blood [28]. We assumed that other, still unknown, factors confound the net effect of physical activity interventions on Lp(a) levels.

Lately, there has been increased interest in the effects of exercise on inflammation. One could hypothesize that RT may influence low-grade systemic inflammation in T2DM [29]. Although we and other investigators have shown the considerable anti-inflammatory effects of aerobic exercise training in the diabetic population [30], scarce data have not consistently proved those effects after RT [31]. Swift et al. [32] showed non-significant amelioration of CRP after any exercise modality as well as aerobic, resistance or combined training. In the present study, we observed non-significant changes in inflammatory markers, including hsCRP, WBC, fibrinogen levels, after RT program. A plausible explanation is that the volume of RT, required to effectively reduce inflammatory milieu in these high-risk subjects, was lower than the minimum recommended. Moreover, it is likely that there is a complex interconnection between body composition, obesity-induced metabolic disorders, and inflammation. Thus, interventions conferring weight-loss or even favorable body composition changes may result in beneficial changes in inflammatory mediators [33]. Future studies will clarify whether such anti-inflammatory effects may be partially driven by weight-loss, the improvement of body composition, or the metabolic adaptations per se [34, 35].

The principal limitation of our study was the small number of patients in each group. In order to restrict patients' disparity, we recruited subjects with poor glycemic control, but on the same oral anti-diabetic regimen. Another limitation of our study was the usage of HOMA-IR, which reflects both peripheral and hepatic insulin sensitivity. However, it is quite difficult to perform euglycemic clamp as a monitoring test in clinical studies. Perhaps the results of our RT might have been underestimated since the control group received a periodical exercise counseling. The latter is common in clinical practice, since the vast majority of overweight diabetic patients periodically receive instructions for better lifestyle, but a low proportion of them, succeed a temporary lifestyle change. The enrolment of exclusively sedentary patients might have revealed more differences.

In conclusion, RT program at moderate-intensity appeared to improve glycemic control, alleviate insulin resistance and reduce ApoB/ApoA-I ratio in individuals with T2DM, but without overt CVD. RT is a feasible and potentially home-based modality of exercise. Despite the lack of significant benefits in Lp(a), inflammatory markers, body composition and cardiorespiratory capacity, our results indicate a partially beneficial influence of RT on metabolic profile of diabetic patients, which needs further investigation.

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References

1. J.B. Buse, H.N. Ginsberg, G.L. Bakris, N.G. Clark, F. Costa, R. Eckel, V. Fonseca, H.C. Gerstein, S. Grundy, R.W. Nesto, M.P. Pignone, J. Plutzky, D. Porte, R. Redberg, K.F. Stitzel, N.J. Stone, Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care **30**, 162–172 (2007)
2. D. Umpierre, P.A. Ribeiro, C.K. Kramer, C.B. Leitão, A.T. Zucatti, M.J. Azevedo, J.L. Gross, J.P. Ribeiro, B.D. Schaan, Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA **305**, 1790–1799 (2011)
3. S.R. Colberg, C.R. Grieco, Exercise in the treatment and prevention of diabetes. Curr. Sports Med. Rep. **8**, 169–175 (2009)

4. N.P. Kadoglou, F. Iliadis, C.D. Liapis, D. Perrea, N. Angelopoulou, M. Alevizos, Beneficial effects of combined treatment with rosiglitazone and exercise on cardiovascular risk factors in patients with type 2 diabetes. Diabetes Care **30**, 2242–2244 (2007)
5. N.P. Kadoglou, I.S. Vrabas, N. Sailer, A. Kapelouzou, G. Fotiadis, G. Noussios, P.E. Karayannacos, N. Angelopoulou, Exercise ameliorates serum MMP-9 and TIMP-2 levels in patients with type 2 diabetes. Diabetes Metab. **36**, 144–151 (2010)
6. H.R. Kwon, K.A. Han, Y.H. Ku, H.J. Ahn, B.K. Koo, H.C. Kim, K.W. Min, The effects of resistance training on muscle and body fat mass and muscle strength in type 2 diabetic women. Korean Diabetes J. **34**, 101–110 (2010)
7. C. Gavin, R.J. Sigal, M. Cousins, M.L. Menard, M. Atkinson, F. Khandwala, G.P. Kenny, S. Proctor, T.C. Ooi, Diabetes Aerobic and Resistance Exercise (DARE) trial investigators. Resistance exercise but not aerobic exercise lowers remnant-like lipoprotein particle cholesterol in type 2 diabetes: a randomized controlled trial. Atherosclerosis **213**, 552–557 (2010)
8. D. Hansen, P. Dendale, L.J. van Loon, R. Meeusen, The impact of training modalities on the clinical benefits of exercise intervention in patients with cardiovascular disease risk or type 2 diabetes mellitus. Sports Med. **40**, 921–940 (2010)
9. A. Chudyk, R.J. Petrella, Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. Diabetes Care **34**, 1228–1237 (2011)
10. J. Leiviskä, J. Sundvall, G. Alfthan, M. Jauhiainen, V. Salomaa, Apolipoprotein A-I, apolipoprotein B, and apolipoprotein B/apolipoprotein A-I ratio: reference intervals compared with values in different pathophysiological conditions from the FINRISK 2007 study. Clin. Chim. Acta **412**, 1146–1150 (2011)
11. M.R. Taskinen, P.J. Barter, C. Ehnholm, D.R. Sullivan, K. Mann, J. Simes, J.D. Best, S. Hamwood, A.C. Keech, FIELD study investigators. Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes. Diabetologia **53**, 1846–1855 (2010)
12. A.N. Qasim, S.S. Martin, N.N. Mehta, M.L. Wolfe, J. Park, S. Schwartz, M. Schutta, N. Iqbal, M.P. Reilly, Lipoprotein(a) is strongly associated with coronary artery calcification in type-2 diabetic women. Int. J. Cardio. **l150**, 17–21 (2011)
13. M.T. Wallace, C.J. Levy, R.D. Matthews, Use and abuse of HOMA modeling. Diabetes Care **27**, 1487–1495 (2004)
14. W.R. Sukala, R. Page, D.S. Rowlands, J. Krebs, I. Lys, M. Leikis, J. Pearce, B.S. Cheema, South Pacific Islanders resist type 2 diabetes: comparison of aerobic and resistance training. Eur. J. Appl. Physiol. **112**, 317–325 (2012)
15. D.W. Dunstan, R.M. Daly, N. Owen, D. Jolley, M. De Courten, J. Shaw, P. Zimmet, High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care **25**, 1729–1736 (2002)
16. T.S. Church, S.N. Blair, S. Cocreham, N. Johannsen, W. Johnson, K. Kramer, C.R. Mikus, V. Myers, M. Nauta, R.Q. Rodarte, L. Sparks, A. Thompson, C.P. Earnest, Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA **304**, 2253–2262 (2010)
17. E. Cauza, U. Hanusch-Enserer, B. Strasser, B. Ludvik, S. Metz-Schimmerl, G. Pacini, O. Wagner, P. Georg, R. Prager, K. Kostner, A. Dunky, P. Haber, The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus. Arch. Phys. Med. Rehabil. **86**, 1527–1533 (2005)
18. S. Terada, T. Yokozeki, K. Kawanaka, K. Ogawa, M. Higuchi, O. Ezaki, I. Tabata, Effects of high-intensity swimming training on GLUT-4 and glucose transport activity in rat skeletal muscle. J. Appl. Physiol. **90**, 2019–2024 (2001)
19. G.A. Kelley, K.S. Kelley, Progressive resistance exercise and resting blood pressure: a meta-analysis of randomized controlled trials. Hypertension **35**, 838–843 (2000)
20. B. Strasser, U. Siebert, W. Schobersberger, Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports Med. **40**, 397–415 (2010)
21. C.M. Ballantyne, T.C. Andrews, J.A. Hsia, J.H. Kramer, C. Shear, ACCESS Study Group. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme a reductase inhibitors on non-high-density lipoprotein cholesterol levels. Am. J. Cardiol. **88**, 265–269 (2001)
22. W.C. Cromwell, T.A. Barringer, Low-density lipoprotein and apolipoprotein B: clinical use in patients with coronary heart disease. Curr. Cardiol. Rep. **11**, 468–475 (2009)
23. G. Walldius, I. Jungner, I. Holme, A. Aastveit, W. Kolar, E. Steiner, High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet **358**, 2026–2033 (2001)
24. N.P. Kadoglou, F. Iliadis, N. Sailer, Z. Athanasiadou, I. Vitta, A. Kapelouzou, P.E. Karayannacos, C.D. Liapis, M. Alevizos, N. Angelopoulou, I.S. Vrabas, Exercise training ameliorates the effects of rosiglitazone on traditional and novel cardiovascular risk factors in patients with type 2 diabetes mellitus. Metabolism **59**, 599–607 (2010)
25. M. Stolinski, S. Alam, N.C. Jackson, F. Shojaee-Moradie, C. Pentecost, W. Jefferson, E.R. Christ, R.H. Jones, A.M. Umpleby, Effect of 6-month supervised exercise on low-density lipoprotein apolipoprotein B kinetics in patients with type 2 diabetes mellitus. Metabolism **57**, 1608–1614 (2008)
26. M. Rigla, J.L. Sánchez-Quesada, J. Ordóñez-Llanos, T. Prat, A. Caixàs, O. Jorba, J.R. Serra, A. de Leiva, A. Pérez, Effect of physical exercise on lipoprotein(a) and low-density lipoprotein modifications in type 1 and type 2 diabetic patients. Metabolism **49**, 640–647 (2000)
27. S.Y. Jae, K.S. Heffernan, M.K. Lee, B. Fernhall, W.H. Park, Relation of cardiorespiratory fitness to inflammatory markers, fibrinolytic factors, and lipoprotein(a) in patients with type 2 diabetes mellitus. Am. J. Cardiol. **102**, 700–703 (2008)
28. L.T. Mackinnon, L.M. Hubinger, Effects of exercise on lipoprotein(a). Sports Med. **28**, 11–24 (1999)
29. L.K. Stewart, M.G. Flynn, W.W. Campbell, B.A. Craig, J.P. Robinson, K.L. Timmerman, B.K. McFarlin, P.M. Coen, E. Talbert, The influence of exercise training on inflammatory cytokines and C-reactive protein. Med. Sci. Sports Exerc. **39**, 1714–1719 (2007)
30. N.P. Kadoglou, F. Iliadis, N. Angelopoulou, D. Perrea, G. Ampatzidis, C.D. Liapis, M. Alevizos, The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. Eur. J. Cardiovasc. Prev. Rehabil. **14**, 837–843 (2007)
31. A. Chudyk, R.J. Petrella, Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. Diabetes Care **34**, 1228–1237 (2011)
32. D.L. Swift, N.M. Johannsen, C.P. Earnest, S.N. Blair, T.S. Church: Effect of exercise training modality on C-reactive protein in type-2 diabetes. Med. Sci. Sports Exerc. (2011) (Epub ahead of print)
33. H.E. Ploeger, T. Takken, M.H. de Greef, B.W. Timmons, The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: a systematic review. Exerc. Immunol. Rev. **15**, 6–41 (2009)
34. S. Balducci, S. Zanuso, A. Nicolucci, F. Fernando, S. Cavallo, P. Cardelli, S. Fallucca, E. Alessi, C. Letizia, A. Jimenez, F.

Fallucca, G. Pugliese, Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr. Metab. Cardiovasc. Dis. **20**, 608–617 (2010)

35. C.L. Clarson, F.H. Mahmud, J.E. Baker, H.E. Clark, W.M. McKay, V.D. Schauteet, D.J. Hill, Metformin in combination with structured lifestyle intervention improved body mass index in obese adolescents, but did not improve insulin resistance. Endocrine **36**, 141–146 (2009)