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# The use of statins potentiates the insulin-sensitizing effect of exercise training in obese males with and without Type 2 diabetes

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## A B S T R A C T

Exercise training is advocated in insulin resistance and statins are used to treat hyperlipidaemia, two cardiometabolic risk factors often presenting concurrently. Statin intake may blunt mitochondrial function and the adaptive response to exercise training. Thus combining exercise training with statin administration may have adverse effects. We examined whether improvements in cardiometabolic risk factors, insulin sensitivity and mitochondrial function mediated by progressive exercise training are affected by statin use. A group of 14 obese elderly males on statins (ST) and 22 matched control subjects (C) were examined. Results on *in vivo* mitochondrial function [MRS (magnetic resonance spectroscopy)], mitochondrial density (Western blotting), insulin sensitivity (clamp) and metabolic flexibility (indirect calorimetry) were compared before and after a 12-week combined progressive exercise training programme (3 × per week; 45 min per session). Except for LDL (low-density lipoprotein) cholesterol, all pre-training values were comparable between statin users and control subjects. *In vivo* mitochondrial function and mitochondrial density improved by training in both groups. Interestingly, blood-lipid profile, insulin sensitivity (+72%), non-oxidative and oxidative glucose disposal (+38% and +112%) and insulin-mediated suppression of fat oxidation (−62%) improved only in the ST group. We conclude that statin treatment did not impede exercise performance or tolerance, mitochondrial function or mass. In addition, training-induced improvements in glucose homeostasis were preserved in the ST group. Strikingly, the insulin-sensitizing effect of training was more prominent in the ST group than in the C group. The combined prescription of statins along with exercise training is safe and should be considered for subjects prone to develop insulin resistance.

## INTRODUCTION

Hyperlipidaemia and hyperglycaemia are frequently reported in obese subjects and are highly associated

with the development of cardiovascular disorders, the primary cause of death in obesity. Whereas treatment with HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors, like statins, is often prescribed in

**Key words:** cardiometabolic risk-factor, exercise training, insulin sensitivity, mitochondrial function, statin, Type 2 diabetes.

**Abbreviations:** AU, arbitrary unit; BMI, body mass index; EGP, endogenous glucose production; HbA<sub>1c</sub>, glycated haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MRS, magnetic resonance spectroscopy; MVC, maximal voluntary contraction; PCr, phosphocreatine; Ra, rate of glucose appearance; Rd, rate of glucose disposal; RER, respiratory exchange ratio; T2D, Type 2 diabetes;  $\dot{V}CO_2$ , carbon dioxide production;  $\dot{V}O_2$ , oxygen consumption;  $\dot{V}O_{2max}$ , maximal  $\dot{V}O_2$ .

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cases of hyperlipidaemia [1,2], implementing routine physical exercise in daily life is advocated in treatment of hyperglycaemia [3]. Hyperlipidaemia and hyperglycaemia, however, often present concurrently. Hence, combining the current guidelines would imply combining statin treatment with physical exercise. Guidelines released recently from the American Diabetes Association state that in diabetic individuals >40 years of age, statins use should be added to lifestyle therapy in order to reach target levels of LDL (low-density lipoprotein) cholesterol <2.6 mmol/l in patients with T2D (Type 2 diabetes) or <1.80 mmol/l in T2D with established CVD (cardiovascular disease) [4]. The use of statins, however, has been associated with myotoxicity, mitochondrial dysfunction [5–9] and muscular damage [7,10]. In addition, it has been suggested that statin use may blunt the adaptive response to exercise training [11,12].

To examine the role of statins in exercise-training-mediated improvements in cardiometabolic risk factors, markers of *in vivo* mitochondrial function and insulin sensitivity were evaluated after 12 weeks of training in a group of elderly male obese healthy and T2D subjects, stratified to the use of statins.

## MATERIALS AND METHODS

### Subject recruitment and stratification

Initially, we recruited 38 sedentary elderly male obese subjects, of whom 18 subjects had been diagnosed with T2D for at least one year [13]. Diabetic patients had well-controlled diabetes [ $\text{HbA}_{1c}$  (glycated haemoglobin) =  $\pm 7.2\%$ ] and were using oral anti-diabetic agents [metformin only, or in combination with SU (sulfonylurea) derivatives]. The other 20 subjects were categorized as normoglycaemic. Glycaemic control was checked for by measuring  $\text{HbA}_{1c}$ , and glucose tolerance by performing an oral glucose tolerance test. Subjects were informed about the nature and risks of the experimental procedures before their written informed consent was obtained. The study has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the institutional medical ethical committee.

Retrospectively, the entire group of 38 subjects was stratified according to the use of statins. Two subjects on fibrates were excluded from the analysis. Statin use was defined as using any type of statins for over a year at the onset of the study, irrespective of dosage. Individual data on statin use can be found in the Supplementary Table S1 at <http://www.clinsci.org/cs/119/cs1190293add.htm>. Stratification resulted in 14 subjects on statins (ST group) and 22 subjects without statin treatment (C group) with eight T2D subjects in both groups. None of the baseline characteristics was significantly different between the

C and ST groups, except for LDL cholesterol which was lower in the patients using statins (Table 1). To examine whether the type of statin and the dosage used may have affected the outcome of the present study, we ranked the statins on their reported LDL lowering potency, taking into account the dosage used. Using this marker of potency as an independent variable we performed correlative analysis with all parameters under investigation.

### Exercise training protocol

All subjects were engaged in an exercise programme for 12 weeks, consisting of a combination of aerobic and resistance exercise. Subjects were monitored extensively during the training period and attention has been paid to follow up conversations with respect to their motivation. Aerobic exercise was carried out on a cycling ergometer twice a week for 30 min at 55% of their previously determined maximal work load. Training sessions took place in small groups of 3–4 persons and, as a measure of exercise intensity, heart rate was monitored and registered in a training diary at 5 min intervals. Maximal workload was re-evaluated after 6 weeks of training and training load was adjusted accordingly.

Resistance exercise was performed once a week for 40 min. The training involved a ‘circuit’ of eight exercises, focussing on large muscle groups (i.e. chest press, leg extension, latissimus dorsi pull down, leg press, triceps curl, biceps curl, crunches and horizontal row). A first series of eight repetitions was performed at 55% of their pre-determined MVC (maximal voluntary contraction), followed by two series of eight repetitions at 75% MVC [13]. Resistance training was given individually and MVC was re-assessed every 4 weeks.

### Hyperinsulinaemic–euglycaemic clamp

Dietary habits were stable, physical exercise was avoided for the 2 days prior to the clamp procedure and anti-diabetic medication was withdrawn 7 days prior to the clamp. The use of statins was continued throughout the study. Insulin sensitivity was measured by a 3 h hyperinsulinaemic–euglycaemic clamp, before and after the training period. A primed constant infusion of glucose tracer ( $[6,6\text{-}^2\text{H}_2]\text{glucose}$ ) was initiated at  $t=0$  min to determine non-insulin stimulated  $R_a$  (rate of glucose appearance) and  $R_d$  (rate of glucose disposal). At  $t=180$  min, the actual clamp procedure was started with a primed constant infusion of insulin ( $40 \text{ m-units} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ ) [13]. EGP (endogenous glucose production) was calculated as  $R_a$  minus exogenous glucose infusion rate. Non-oxidative glucose disposal was calculated as  $R_d$  minus carbohydrate oxidation. In the non-insulin-stimulated period ( $t=150\text{--}180$  min) and under steady clamp conditions ( $t=330\text{--}360$  min), blood samples and indirect calorimetry measurements (ventilated hood) were obtained. A needle muscle biopsy

**Table 1 Subject characteristics**Results are expressed as mean  $\pm$  S.E.M. \*Post-training significantly different from pre-training; #ST group significantly different from C group.

Subject characteristics	C group		ST group	
	Pre-training	Post-training	Pre-training	Post-training
Age (years)	59.2 $\pm$ 1.0		58.4 $\pm$ 0.9	
Subjects diagnosed with diabetes ( <i>n</i> )	8		8	
Weight (kg)	94.9 $\pm$ 2.8	94.4 $\pm$ 2.9	93.2 $\pm$ 3.2	91.9 $\pm$ 3.1
Height (cm)	177.6 $\pm$ 1.3		177.2 $\pm$ 1.5	
BMI (kg $\cdot$ m <sup>-2</sup> )	30.1 $\pm$ 0.8	30.0 $\pm$ 0.9	30.0 $\pm$ 0.9	29.6 $\pm$ 0.8
Body fat (%)	32.4 $\pm$ 1.3	31.6 $\pm$ 1.3*	29.6 $\pm$ 1.8	28.4 $\pm$ 1.8
Fat mass (kg)	31.2 $\pm$ 1.8	30.4 $\pm$ 1.8*	27.9 $\pm$ 2.3	26.4 $\pm$ 2.2
Fat-free mass (kg)	64.5 $\pm$ 1.9	64.9 $\pm$ 1.9	65.3 $\pm$ 2.1	65.5 $\pm$ 2.1
$\dot{V}O_2$	28.6 $\pm$ 1.1	30.5 $\pm$ 1.2*	28.5 $\pm$ 1.4	31.7 $\pm$ 1.7*
Work max. (Watt)	208 $\pm$ 9	236 $\pm$ 9*	201 $\pm$ 10	231 $\pm$ 10*
Average strength (kg)	83.5 $\pm$ 3.2	102.9 $\pm$ 3.7*	87.4 $\pm$ 4.0	105.3 $\pm$ 4.4*
Fasting glucose (mmol/l)	7.2 $\pm$ 0.4	6.9 $\pm$ 0.4	7.5 $\pm$ 0.5	7.3 $\pm$ 0.6
HbA <sub>1c</sub> (%)	6.4 $\pm$ 0.2	6.3 $\pm$ 0.2	6.6 $\pm$ 0.3	6.7 $\pm$ 0.3
Triacylglycerols (mmol/l)	1.6 $\pm$ 0.1	1.6 $\pm$ 0.2	1.7 $\pm$ 0.2	1.6 $\pm$ 0.1
Total cholesterol (mmol/l)	5.4 $\pm$ 0.1	5.2 $\pm$ 0.2	5.0 $\pm$ 0.2	4.6 $\pm$ 0.2*
LDL (mmol/l)	3.5 $\pm$ 0.1	3.3 $\pm$ 0.2	2.9 $\pm$ 0.2#	2.7 $\pm$ 0.2#
HDL (mmol/l)	1.2 $\pm$ 0.0	1.2 $\pm$ 0.1	1.3 $\pm$ 0.1	1.3 $\pm$ 0.1
hsCRP (mg/l)	2.0 $\pm$ 0.3	1.8 $\pm$ 0.3	1.6 $\pm$ 0.5	1.6 $\pm$ 0.5

was obtained from the vastus lateralis muscle before starting the tracer infusion.

### Blood sample analysis

Blood was sampled and analysed as described previously [13]. Concentrations of total cholesterol (ABX Diagnostics), HDL (high-density lipoprotein) cholesterol (precipitation method; Roche Diagnostics), and triacylglycerols (triglycerides) corrected for free glycerol (Sigma–Aldrich) were analysed enzymatically. Serum LDL cholesterol concentrations were calculated by using the formula of Friedewald. hsCRP (high-sensitivity C-reactive protein) was measured on a Roche Cobas Mira random access biochemistry analyser with a commercially available kit (Kamiya Biomedical Company).

### Metabolic flexibility

Metabolic flexibility is the ability to switch from predominantly fat oxidation in the fasted state to glucose oxidation under insulin-stimulated conditions [14]. Metabolic flexibility was expressed as the change in RER (respiratory exchange ratio) from the fasted state to the insulin-stimulated condition. Substrate oxidation was calculated according to the method of Frayn [15] with protein oxidation considered negligible: carbohydrate oxidation rate ( $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$ ) =  $(4585 \times \dot{V}CO_2) - (3226 \times \dot{V}O_2)$ /body weight/180  $\times$  1000; where  $\dot{V}CO_2$  is carbon dioxide production and  $\dot{V}O_2$  is oxygen consumption) and lipid

oxidation rate ( $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$ ) =  $(1695 \times \dot{V}O_2 - 1701 \times \dot{V}CO_2)$ /body weight/860  $\times$  1000 [15].

### MRS (magnetic resonance spectroscopy)-based measurement of mitochondrial function

Maximal muscle strength during one-legged knee-extension exercise was assessed a few days prior to the actual <sup>31</sup>P-MRS measurement with an incremental protocol in an MRS compatible exercise device. During this test subjects were asked to perform knee-extensions at 0.5 Hz, while increasing the load to be lifted every 30 s by 500 g, with an initial weight of 5 kg. The test was performed until exhaustion or until the frequency of 0.5 Hz could no longer be maintained (maximal load). The PCr (phosphocreatine)-lowering exercise session during the test-day was performed at 60% of this pre-determined load.

Baseline <sup>31</sup>P-MRS measurements were performed on a 1.5 T whole-body scanner (Intera; Philips Health Care). A 6-cm surface coil was used for localization and was fixed in the middle of the vastus lateralis muscle. A series of partially saturated spectra (free induction decays) was acquired (TR = 4 s; 1 measurement; spectral bandwidth 1500 Hz; adiabatic pulse). Knee extension exercise was performed at 0.5 Hz to an acoustic cue on a home-built magnetic resonance compatible ergometer with a pulley system. The PCr-lowering exercise was performed with identical weights before and after training.

The acquisition time during the time series was structured as follows: 40 s of rest, 5 min of knee-extension exercise and 5 min of recovery. After application of phase correction, line-broadening and DC (direct conversion) correction, spectra were fitted in the time domain with the AMARES algorithm [16] in the jMRUI software [17] using prior knowledge. Five peaks were fitted with Gaussian curves ( $P_i$ , PCr, and 3 ATP peaks) in the partially saturated spectra of the time series. To determine the pH during the exercise period, five consecutive spectra of the time series were added and the pH was calculated in jMRUI from the frequency shift between the PCr and  $P_i$  peaks. The time-course of the PCr amplitude [PCr( $t$ )] during the last 20 s of exercise (steady state) and during the recovery period was fitted with MATLAB software (Mathworks) as described previously [18], assuming a mono-exponential PCr recovery. Post-exercise PCr resynthesis rate is an almost exclusively oxidative process and is hence a good reflection of mitochondrial oxidative function. The rate constant of the monoexponential recovery is given. The higher the rate constant ( $s^{-1}$ ), the better *in vivo* mitochondrial function.

### Mitochondrial density

Five different structural components of the electron transport chain were measured at the protein level as a reflection of mitochondrial density [13]. The ND6 subunit of complex I, the 30-kDa Ip subunit of complex II, the 47-kDa core protein 2 of complex III, COXII (cytochrome *c* oxidase subunit II) and the  $F_0F_1$  ATP synthase subunit (complex V) were measured using a monoclonal antibody cocktail of five monoclonal antibodies directed against the subunits mentioned (MitoSciences) as previously described [19]. As these subunits differ considerably in molecular mass, this antibody gives five distinct bands in human samples. Each individual band reflects one of the mitochondrial subunits. In short, muscle biopsies were homogenized in ice-cold Tris/EDTA buffer at pH 7.4, and then the homogenates were sonicated for 15 s. Subsequently, two volumes of each skeletal muscle homogenate and one volume of SDS sample buffer were boiled for 4 min. Next, 13% polyacrylamide gels containing 0.1% SDS were loaded with equal amounts of protein from each sample, and electrophoresis was performed using a Mini-Protean 3 Electrophoresis Cell (Bio-Rad Laboratories). After electrophoresis, the gel was scanned and then subjected to densitometry analysis for all of the individual bands (per subject per subunit). To adjust for inter-gel variation, the densitometry of the band of interest per subject was normalized to the mean densitometry of the complete gel. Protein content is expressed as AUs (arbitrary units).

### Statistics

Statistical analyses were performed two-sided using SPSS for Windows 15.0 software (SPSS). Statistical

significance was set at  $P < 0.05$ . A two-way ANOVA model for repeated measures was applied using control and statin users as between subject variables and pre- and post-training data as repeated within subject variables. Differential responses between the ST and C groups were examined using the interaction terms. In addition, in the case of a significant training effect, differential responses of T2D and healthy subjects within the ST and C groups were examined.

## RESULTS

### Subjects

Before training, body weight ( $94.9 \pm 2.8$  and  $93.2 \pm 3.2$  kg), BMI (body mass index) ( $30.1 \pm 0.8$  and  $30.0 \pm 0.9$  kg  $\cdot$  m $^{-2}$ ), and age ( $59.2 \pm 1.0$  and  $58.4 \pm 0.9$  years) were comparable in the C and ST groups respectively. Training did not alter body weight and BMI in the C group, whereas body weight, but not BMI, tended to decline in the ST group (from  $93.2 \pm 3.2$  to  $91.9 \pm 3.1$  kg,  $P = 0.09$ , and from  $30.0 \pm 0.9$  to  $29.6 \pm 0.8$  kg  $\cdot$  m $^{-2}$  respectively). Fat mass declined in the C group (from  $31.2 \pm 1.8$  to  $30.4 \pm 1.8$  kg after training,  $P = 0.02$ ), whereas there was a tendency towards a decreased fat mass in the ST group (from  $27.9 \pm 2.3$  to  $26.4 \pm 2.2$  kg after training;  $P = 0.10$ ). Fat-free mass was similar between both groups and was unaffected by training.

Before training,  $\dot{V}O_{2max}$  (maximal  $\dot{V}O_2$ ) and maximal workload was comparable in both groups ( $\dot{V}O_{2max}$  of  $28.6 \pm 1.0$  ml  $\cdot$  kg $^{-1}$  of body weight  $\cdot$  min $^{-1}$  and  $27.7 \pm 1.5$  ml  $\cdot$  kg $^{-1}$  of body weight  $\cdot$  min $^{-1}$  in the C and ST groups respectively,  $P = 0.63$ ; workload,  $208 \pm 9$  W and  $201 \pm 10$  W in the C and ST groups respectively,  $P = 0.61$ ). Exercise training improved  $\dot{V}O_{2max}$  and maximal workload significantly and to the same extent in the C and ST groups ( $\dot{V}O_{2max}$  by  $+7.0 \pm 2.2\%$  and  $+11.7 \pm 3.2\%$  in the C and ST groups respectively,  $P < 0.01$ ; workload by  $+14.6 \pm 2.7\%$  and  $+16.1 \pm 2.3\%$  in the C and ST groups respectively,  $P < 0.01$ ). Muscle strength was comparable before training ( $83.5 \pm 3.2$  kg and  $87.4 \pm 4.0$  kg in the C and ST groups respectively,  $P = 0.46$ ) and improved significantly and to the same extent in both groups ( $+24.7 \pm 1.9\%$  and  $+21.6 \pm 2.1\%$  in the C and ST groups respectively,  $P < 0.01$ ). On the rare occasion of missing a training session, this session was rescheduled within a week of the original training date. As maximally achieved workload during the maximal test was similar in both groups and the number of training sessions performed was identical, total workload performed during the training sessions across groups was comparable.

### Glucose and insulin profile

Fasting glucose levels (of  $7.2 \pm 0.4$  mmol/l and  $7.5 \pm 0.5$  mmol/l in the C and ST groups respectively) and

HbA<sub>1c</sub> levels (of  $6.4 \pm 0.2\%$  and  $6.6 \pm 0.3\%$  in the C and ST groups respectively) were similar at the onset of the training programme. The 12-week exercise training programme did not change HbA<sub>1c</sub> or fasting glucose levels in either group. Fasting plasma insulin levels did not differ significantly before onset of the training programme between the C and ST groups ( $17.2 \pm 2.0$  compared with  $17.9 \pm 2.0$  m-units/l in the C and ST groups respectively) but decreased significantly in both groups after training (from  $17.2 \pm 2.0$  m-units/l to  $15.7 \pm 1.7$  m-units/l in the C group and from  $17.9 \pm 2.0$  m-units/l to  $15.0 \pm 1.7$  m-units/l in the ST group,  $P < 0.05$  in both groups).

### Lipid profile

Pre-training, insulin-mediated suppression of lipolysis, measured as the drop in plasma non-esterified fatty acid upon insulin infusion, was comparable between groups. Training did not affect insulin-mediated suppression of lipolysis in the C group (suppression pre-training  $81.7 \pm 1.6\%$  compared with  $83.0 \pm 1.5\%$  post-training), but improved significantly in the ST group (from  $77.7 \pm 1.8\%$  to  $82.9 \pm 1.7\%$ ,  $P = 0.01$ ).

Triacylglycerols were comparable between groups and were unaffected by training. Also total cholesterol before training was similar in the C and ST groups. Training reduced total cholesterol significantly in the ST group (from  $5.0 \pm 0.2$  to  $4.6 \pm 0.2$  mmol/l,  $P = 0.03$ ), but not in the C group (from  $5.4 \pm 0.2$  to  $5.2 \pm 0.1$  mmol/l), resulting in a tendency towards lower total cholesterol values in the ST group compared with the C group ( $P = 0.07$ ). LDL cholesterol was significantly higher in the C group compared with the ST group pre-training ( $3.5 \pm 0.1$  mmol/l compared with  $2.9 \pm 0.2$  mmol/l in the C and ST groups respectively,  $P = 0.05$ ) and tended to decline in both groups (from  $3.5 \pm 0.1$  to  $3.3 \pm 0.2$  mmol/l in the C group,  $P = 0.07$ , and from  $2.9 \pm 0.2$  to  $2.7 \pm 0.2$  mmol/l in the ST group,  $P = 0.07$ ). HDL cholesterol and hsCRP was comparable in the C and ST groups and was unaffected by training (Table 1).

### Whole-body insulin-stimulated glucose uptake

Insulin-stimulated glucose uptake, as determined by the change in the glucose disposal rate during the hyperinsulinaemic-euglycaemic clamp ( $\Delta R_d$ ), was not different between the C and ST groups pre-training ( $12.7 \pm 2.1$  and  $9.5 \pm 2.5$   $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$  in the C and ST groups,  $P = 0.33$ ). The C and ST groups responded differentially to training as indicated by significant interaction ( $P < 0.01$ ).  $\Delta R_d$  did not change after training in the C group (from  $12.7 \pm 2.1$  to  $13.6 \pm 1.9$   $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$ ), but improved significantly in the ST group (from  $9.5 \pm 2.5$  to  $16.3 \pm 2.3$   $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$ ,  $P < 0.01$ ). Non-oxidative glucose disposal (from  $4.7 \pm 2.1$  to  $10.0 \pm 2.1$   $\mu\text{mol} \cdot \text{kg}^{-1}$  of body

weight  $\cdot \text{min}^{-1}$ ,  $P < 0.01$ ), as well as oxidative glucose disposal (from  $4.7 \pm 0.9$  to  $6.5 \pm 0.7$   $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$ ,  $P < 0.01$ ) improved significantly in the ST group upon training, but did not change in the C group (with a significant interaction effect between groups for non-oxidative glucose disposal;  $P < 0.01$ ) (Table 2). Insulin-mediated suppression of endogenous glucose production ( $\Delta\text{EGP}$ ) was comparable pre-training ( $-6.8 \pm 0.8$  and  $-7.1 \pm 1.5$   $\mu\text{mol} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$  in the C and ST groups respectively) and was not significantly affected by training, despite a significant interaction effect (Table 2). Results on insulin and glucose disposal are presented in Table 2.

### Markers of mitochondrial density

Mitochondrial density was evaluated by measuring the levels (protein content) of five structural subunits of the distinct complexes of the electron transport chain. Neither the individual complexes, nor the mean protein content of these complexes revealed a difference in mitochondrial density between the C and ST groups pre-training ( $0.56 \pm 0.10$  and  $0.71 \pm 0.10$  AU in the C and ST groups respectively, not significant). Training resulted in increased mitochondrial density in both groups after training (C group,  $P < 0.01$ ; ST group,  $P = 0.03$ ) (Figure 1A).

### MRS measurement

Pre-training *in vivo* mitochondrial function in the C group was similar to the ST group (rate constant of  $0.034 \pm 0.002$  and  $0.034 \pm 0.003$   $\text{s}^{-1}$  in the C and ST groups respectively), whereas after training *in vivo* mitochondrial function improved 34% and 46% (C group,  $P < 0.01$ ; ST group,  $P = 0.02$ ) (Figure 1B).

### Metabolic flexibility

Prior to training, metabolic flexibility ( $P = 0.51$ ), insulin-stimulated glucose oxidation ( $\Delta\text{carbohydrate oxidation}$ ,  $P = 0.99$ ) and suppressed fat oxidation ( $\Delta\text{Fat oxidation}$ ,  $P = 0.47$ ) was comparable between the C and ST groups (Figures 1C and 1D). Exercise training did not affect metabolic flexibility in the C group ( $\Delta\text{RER}$  from  $0.071 \pm 0.008$  to  $0.083 \pm 0.011$ ,  $P = 0.22$ ), whereas metabolic flexibility improved significantly in the ST group ( $\Delta\text{RER}$  from  $0.062 \pm 0.012$  to  $0.089 \pm 0.008$ ,  $P = 0.01$ ), reflecting a concomitant increase in insulin-stimulated glucose oxidation ( $P = 0.01$ ) (Figure 1C) and suppression of fat oxidation ( $P = 0.01$ ) (Figure 1D).

## DISCUSSION

We examined the effect of exercise training on cardiometabolic risk factors, markers of *in vivo* mitochondrial function and insulin sensitivity in male obese elderly with and without T2D who were on

**Table 2** Substrate kinetics pre- and post-training

Results are expressed as means  $\pm$  S.E.M. \*Post-training significantly different from pre-training; § significant interaction effect between C and ST groups. NOGD, non-oxidative glucose disposal.

Substrate	C group		ST group	
	Pre-training	Post-training	Pre-training	Post-training
Plasma insulin (m-units/l)				
Basal	17.2 $\pm$ 2.0	15.7 $\pm$ 1.7*	17.9 $\pm$ 2.0	15.0 $\pm$ 1.7*
Clamp	109.4 $\pm$ 5.4	107.8 $\pm$ 4.2	111.2 $\pm$ 4.5	107.9 $\pm$ 5.1
Plasma non-esterified fatty acid ( $\mu$ mol/l)				
Basal	498.6 $\pm$ 18.3	498.7 $\pm$ 31.1	473.3 $\pm$ 31.0	421.4 $\pm$ 27.9
Clamp	90.2 $\pm$ 7.7	81.5 $\pm$ 8.2	103.9 $\pm$ 10.0	71.1 $\pm$ 8.3*§
Rd glucose ( $\mu$ mol $\cdot$ kg <sup>-1</sup> of body weight $\cdot$ min <sup>-1</sup> )				
Basal	10.0 $\pm$ 0.8	8.7 $\pm$ 0.7	10.9 $\pm$ 0.9	8.7 $\pm$ 0.7*
Clamp	22.7 $\pm$ 2.0	22.3 $\pm$ 2.1	20.3 $\pm$ 2.2	25.0 $\pm$ 2.1*§
Delta	12.7 $\pm$ 2.1	13.6 $\pm$ 1.9	9.5 $\pm$ 2.5	16.3 $\pm$ 2.3*§
EGP ( $\mu$ mol $\cdot$ kg <sup>-1</sup> of body weight $\cdot$ min <sup>-1</sup> )				
Basal	9.7 $\pm$ 0.6	9.3 $\pm$ 0.6	9.7 $\pm$ 0.7	7.9 $\pm$ 0.8
Clamp	2.8 $\pm$ 0.4	0.8 $\pm$ 0.5*	2.7 $\pm$ 1.0	1.8 $\pm$ 1.3
Delta	- 6.8 $\pm$ 0.8	- 8.5 $\pm$ 0.7	- 7.1 $\pm$ 1.5	- 6.5 $\pm$ 1.5§
Carbohydrate oxidation ( $\mu$ mol $\cdot$ kg <sup>-1</sup> of body weight $\cdot$ min <sup>-1</sup> )				
Basal	6.8 $\pm$ 0.5	7.3 $\pm$ 0.5	7.8 $\pm$ 0.8	7.0 $\pm$ 0.5
Clamp	11.5 $\pm$ 0.7	12.9 $\pm$ 0.8	12.6 $\pm$ 1.1	13.5 $\pm$ 0.7
Delta	4.7 $\pm$ 0.7	5.2 $\pm$ 0.8	4.7 $\pm$ 0.9	6.5 $\pm$ 0.7*
NOGD ( $\mu$ mol $\cdot$ kg <sup>-1</sup> of body weight $\cdot$ min <sup>-1</sup> )				
Basal	3.3 $\pm$ 0.8	1.2 $\pm$ 0.6*	3.0 $\pm$ 1.0	1.8 $\pm$ 1.1
Clamp	11.2 $\pm$ 1.5	9.5 $\pm$ 1.8	7.8 $\pm$ 1.9	11.9 $\pm$ 2.*§
Delta	7.9 $\pm$ 1.7	8.4 $\pm$ 1.7	4.7 $\pm$ 2.1	10.0 $\pm$ 2.1*§
Lipid oxidation ( $\mu$ mol $\cdot$ kg <sup>-1</sup> of body weight $\cdot$ min <sup>-1</sup> )				
Basal	1.10 $\pm$ 0.06	1.02 $\pm$ 0.04*	1.06 $\pm$ 0.05	1.15 $\pm$ 0.08
Clamp	0.69 $\pm$ 0.04	0.57 $\pm$ 0.06*	0.71 $\pm$ 0.06	0.60 $\pm$ 0.04
Delta	- 0.41 $\pm$ 0.05	- 0.45 $\pm$ 0.07	- 0.34 $\pm$ 0.07	- 0.55 $\pm$ 0.06*

lipid-lowering drugs (statins, ST group) and compared these effects with a control group (C group) not taking statins.

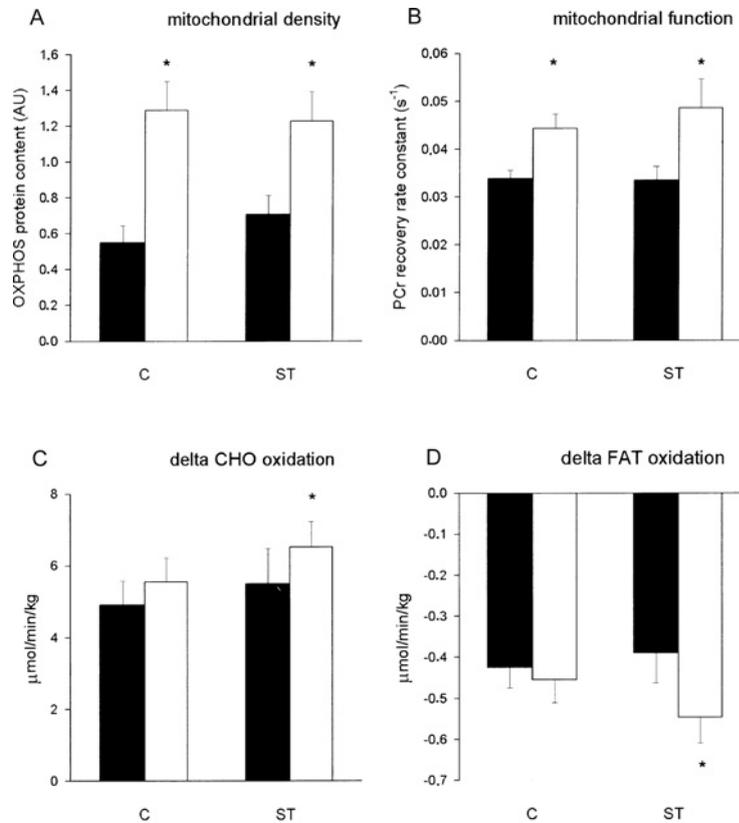
Maximal exercise capacity and markers of mitochondrial content and function were not negatively impacted by statins. In addition, training-induced improvements in markers of cardiometabolic risk, insulin sensitivity and fuel selection were more prominent, and sometimes even exclusively detectable in the ST group compared with the C group. Exercise-training-mediated improvements in mitochondrial density and function were as prominent in the ST group as in the C group. The present study hence shows that exercise prescription on top of statin treatment is safe and at least as beneficial, and for some parameters even more beneficial, for cardiometabolic health, glucose homeostasis and mitochondrial function than exercise training without statins.

We did not find correlations between statin potency and other parameters, suggesting that the findings do not scale with the dosage or potency of the statin used. Furthermore, no interaction effects were detected

between healthy subjects and diabetic subjects, indicating that differences were not solely specific to healthy or diabetic subjects.

### Pre-training pleiotropic effects of statins

After stratification to the use of statins, both groups were comparable for all subject characteristics, except for LDL cholesterol (Table 1). In addition, markers for insulin sensitivity, substrate metabolism and mitochondrial function were similar (Table 2). Interestingly, this is in contrast with previous studies in rodents [20,21] and humans [22], showing improved insulin-sensitivity on a whole-body level and in liver. Another study reported a decrease in mtDNA (mitochondrial DNA) copy number [8], suggesting that statins may affect these parameters somehow. In a more recent study, however, a high dose of statins (80 mg/day simvastatin) did not affect insulin-mediated glucose disposal, hepatic glucose production and myocellular lipid deposition [23].



**Figure 1 Mitochondrial density and function, and metabolic flexibility in ST and C groups**

(A) Mitochondrial density as determined from the mean of five different structural components of the electron transport chain, measured at the protein level, before (black bars) and after (white bars) training. (B) *In vivo* mitochondrial function as determined by post-exercise PCr recovery rate as described previously [18], before (black bars) and after (white bars) training. Results are expressed as rate constant ( $s^{-1}$ ). A higher rate constant corresponds to a high *in vivo* mitochondrial function. (C and D)  $\Delta$ carbohydrate (CHO) oxidation and  $\Delta$ fat oxidation, measured as the change from the fasted state to the insulin-stimulated state, before (black bars) and after (white bars) training. Results are expressed as means  $\pm$  S.E.M., \*post-training significantly different from pre-training.

### Exercise tolerance on statins

Classical measures of physical fitness were similar in the C and ST groups, which is in line with previous reports [24]. A 12-week interval cycling training programme combined with resistance exercise did not provoke statin-related muscle pain or stiffness and was equally well-tolerated in the C and ST groups. Self-reported muscle-stiffness due to unfamiliar exercise occurred predominantly in the first 1.5 weeks and rapidly disappeared after familiarization with the exercise programme. Training-mediated improvements in exercise capacity were similar in both groups. Hence, the results of the present study do not support the hypothesis that the use of statins provokes muscle pathology or may blunt the adaptive responses to exercise training, as suggested previously [25]. However, the present study applied a tailored progressive exercise training programme to avoid the development of muscle soreness, whereas other investigations applied eccentric exercise and exercise bouts on maximal intensity [11,12], types of exercise prone to the development of muscle soreness. In addition, none of the ST group sub-

jects in the present study reported muscle-related complaints under resting conditions after starting their statin treatment. We can hence not exclude that the subjects in the present study represent a statin-tolerating subgroup and that this may contribute to the fact that none of them experienced muscle-related problems while exercising.

### Post-training pleiotropic effects of statins

In contrast with previous reports in humans [6] we did not detect any (negative) effects of statin use on mitochondrial content and function pre-training and showed similar improvements upon training. It should be noted though, that in the present study the dosage of statins used was in general lower [6].

Intriguingly, exercise training in the ST group improved insulin-stimulated glucose disposal, both by an increase in oxidative, as well as in non-oxidative, glucose disposal, without an effect on hepatic insulin sensitivity. The improvement in non-oxidative glucose disposal is of particular interest, as we previously identified non-oxidative glucose disposal as the non-responsive

culprit for training-mediated improvements in T2D patients [13]. In contrast, in the C group, insulin-stimulated non-oxidative glucose disposal did not improve significantly after training.

One of the characteristics of insulin-resistant muscle is metabolic inflexibility ( $\Delta$ RER). In the present study we observed that metabolic flexibility improved upon training in the ST group, indicating that statin use does not interfere with training-induced metabolic improvements. The improvement in metabolic flexibility was less pronounced (and non-significant) in the C group.

### Putative mechanisms of statin-mediated potentiation of the beneficial effect of exercise training

We strikingly observed that the insulin-sensitizing effects of exercise training were potentiated by the use of statins, but the precise mechanism(s) remains to be established. Candidate mechanisms include a statin-mediated reduction in superoxide-induced cell damage [26], statin-mediated reduction of low-grade inflammation [27] or a reduction in non-esterified fatty acid flux and hepatic fat storage [28] resulting in improved hepatic insulin sensitivity. The present study does not allow conclusions on the putative effects of statins on superoxide production or superoxide-mediated cell damage. Using hsCRP as a marker for low-grade inflammation, we report no differences in low-grade inflammation pre-training between the C and ST groups, and did not detect any training effects on hsCRP. Recently it has been shown that even a high-dose of simvastatin (80 mg daily) does not affect hepatic lipid stores or insulin sensitivity significantly [23]. This is in line with the present study showing similar insulin-mediated suppression of hepatic glucose output pre-training in the C and ST groups.

Many patients taking statins are also taking other drugs targeting cardiovascular risk control. The most clear design to examine the effects of the use of statins on exercise-mediated improvements in glucose homeostasis and cardiovascular risk would be a double-blind, placebo-controlled, randomized clinical trial. A disadvantage, however, would be that only subjects who were not on statins before the start of the study can be included and in daily life patients have usually been taking statins for quite some time even before they are advised to take physical exercise. Hence, we feel that the design of the present study provides a valuable and valid representation of what happens when subjects implement regular exercise in their daily lives, on top of any medication they are taking already. The drawback of our design is that the ST group is not homogeneous for some of the output parameters examined. The fact that we indeed do observe significant differences for the key outcome parameters, however, indicates the effects

reported are strong enough to reach significance, even with the relatively small group size.

In conclusion, the present study shows in elderly males with moderate obesity that statin treatment did not inhibit exercise-induced improvements with respect to mitochondrial density and function. Rather, improvements in total cholesterol, insulin-stimulated lipolysis, insulin sensitivity, non-oxidative glucose disposal, metabolic flexibility and substrate oxidation were more pronounced and/or even exclusively detectable when exercise and statin use was combined. This study suggests that combining physical exercise training in subjects who tolerate statin treatment well under resting conditions may be at least as beneficial, and for some parameters even more beneficial, than exercise training exclusively. Thus the present findings indicate that the recently published guidelines of the American Diabetes Association [29] to prescribe statins to all T2D subjects over the age of 40 can be safely combined with previous guidelines on lifestyle interventions.

### AUTHOR CONTRIBUTION

Ruth Meex performed the experiments and wrote the manuscript; Esther Phielix performed the experiments; Vera Schrauwen-Hinderling performed the MRS experiments; Esther Moonen-Kornips and Gert Schaart performed the analysis of the blood and plasma samples; and Patrick Schauwen and Matthijs Hesselink contributed to the discussions and reviewed/edited the manuscript prior to submission.

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■ SUPPLEMENTARY ONLINE DATA

# The use of statins potentiates the insulin-sensitizing effect of exercise training in obese males with and without Type 2 diabetes

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**Table S1** Statin use of the ST group subjects in the present study

Subject no.	Statin dose	Statin
1	1 × 10 mg	Atorvastatin
2	1 × 20 mg	Simvastatin
3	1 × 5 mg	Rosuvastatin
4	1 × 10 mg	Pravastatin
5	1 × 40 mg	Pravastatin
6	1 × 40 mg	Pravastatin
7	1 × 5 mg	Rosuvastatin
8	2 × 30 mg	Simvastatin
9	1 × 10 mg	Atorvastatin
10	1 × 10 mg	Atorvastatin
11	1 × 5 mg	Rosuvastatin
12	1 × 40 mg	Simvastatin
13	1 × 20 mg	Simvastatin
14	1 × 40 mg	Atorvastatin

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