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Exercise training improves glycemic control in long-standing, insulin-treated type 2 diabetes patients

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Regular exercise represents an effective strategy to prevent and/or treat type 2 diabetes (1; 2). However, the clinical benefits of exercise intervention in a vastly expanding group of long-standing, insulin-treated type 2 diabetes patients with co-morbidities is less evident. As these patients generally experience muscle weakness (3-6), cardiovascular co-morbidities (7-10) and/or exercise intolerance (3; 11-13), it has proven difficult or even impossible for them to adhere to an intense endurance exercise training regimen (14; 15). In the present study, we investigated the feasibility and benefits of a low-impact exercise intervention program, combining both endurance and resistance type exercise, in long-standing, insulin-treated type 2 diabetes patients with a high cardiovascular risk profile. We assessed the impact of 5 months of exercise training on glycemic control, body composition, workload capacity, and whole-body as well as skeletal muscle oxidative capacity.

RESEARCH DESIGN AND METHODS

Eleven male, type 2 diabetes patients volunteered to participate in this study. Participants (age 59±3 y; BMI: 32±1 kg/m^2) had been diagnosed with type 2 diabetes for 12±2 y and had been on exogenous insulin treatment for 7±2 y (insulin requirements: 93±11 IU/d). All participants were sedentary and showed a high cardiovascular risk profile (with a 10-year risk for coronary heart disease of 30±2% according to the UKPDS (16)). Participants had been on a stable regimen of diabetes medication for at least 3 months before recruitment. Type 2 diabetes patients using thiazolidinediones and/or beta-blockers <6 months and participants with impaired liver function, macroalbuminuria, severe retinopathy or cardiovascular problems were excluded.

Before and after the 5 month exercise program body composition (DXA), upper leg muscle volume (MRI), glycemic control, blood lipid profile, blood pressure, whole-body oxygen uptake and maximal workload capacity, intramyocellular lipid content (IMCL) and skeletal muscle oxidative capacity were assessed. Plasma glucose, HbA_{1c}, serum cholesterol, HDL-cholesterol, non-esterified fatty acid, triacylglycerol, adiponectin, TNF-α, HsCRP, and C-peptide concentrations were determined in fasting blood. Blood pressure was recorded during supine rest using an automatic blood pressure measuring device. Mean arterial blood pressure (MAP) was calculated from the last 3 stable blood pressure measurements over a 10 min period. Blood pressure lowering medications were not changed throughout the study. Whole-body oxygen uptake capacity (VO_{2max}) and maximal workload capacity (W_{max}) were measured during an incremental exercise test to exhaustion. MR spectroscopy (MRS) measurements were performed using a 1.5-Tesla whole-body MR-scanner. Localized ^{1}HMRS was used to measure IMCL in the *Musculus (M.) vastus lateralis.* ^{31}PMRS was applied to measure post-exercise phosphocreatine (PCr) recovery as described previously (17). Results are expressed as the time constant of recovery for PCr and ADP, i.e. τ_{PCr} and τ_{ADP}, representing skeletal muscle oxidative capacity (18).

The backbone of the exercise program was progressive resistance training (PRT), with high-intensity interval training (HIT) as a supplement. Four bouts of resistance type exercise targeting the upper-body were performed (2×10 reps, 50% of 1 repetition max (1RM) (19)). Thereafter, resistance training was continued with horizontal leg press and leg extension (2×10 reps). Throughout the PRT, the intensity was progressively increased from 50-80% 1RM. In each session, PRT was followed by multiple bouts of HIT to stress working leg muscle without overloading the cardiovascular system (20). Both the

number of bouts and work-rate for the interval modes were progressively increased. The HIT included 4-8 cycling bouts of 30/60 s at 50-60% W_{max} (20). Exercise sessions required ~45 min to complete and were performed 3 times a week. All data are presented as mean±standard error of the mean (SEM). Paired samples T-tests (two-sided) were applied to evaluate changes following exercise intervention. Statistical significance was set at $P \leq 0.05$.

RESULTS

All participants completed the exercise training program and showed an 83±4% attendance rate for the supervised training sessions. Exercise training resulted in a decline in truncal fat mass and an increase in lean leg muscle mass (Table 1). Glycemic control improved, with a significant decline in both fasting blood glucose concentration and HbA_{1c} (from 7.6±0.3 to 7.2±0.2%). Exogenous insulin requirements did not change throughout the training program. When calculating the slope of daily insulin requirement over time, it changed from on average +6.69 IU/6 months in the 3 y prior to intervention to -1.6 IU/6 months ($P<0.01$) following the beginning of the program. MAP declined from 106±2 to 98±3 mmHg, systolic pressure tended to decrease from 147±4 to 138±5 mmHg ($P=0.06$). Both maximal power output (1.6±0.1 to 1.9±0.2 W/kg body mass; $P<0.01$) and muscle strength (1RM of 5 exercises: 77±4 to 90±6 kg; $P<0.01$) increased significantly. No changes were observed in the lipid profile, or in the inflammation markers.

CONCLUSIONS

A combination of low-impact endurance and resistance type exercise training is preferred for long-standing, insulin-treated, type 2 diabetes patients, as it provides a relatively low cardiovascular challenge (21) and improves functional performance (22; 23). The present study shows that such an exercise regimen is well tolerated, with all patients being able to complete the program. Combined endurance and resistance type exercise training effectively improves glycemic control, body composition, blood pressure, muscle strength, and workload capacity, and attenuates the progressive increase in exogenous insulin requirements. Although selection bias and sample size should be acknowledged when generalizing the outcome of this study, we conclude that low impact, endurance and resistance type exercise training should be prescribed in the vastly expanding population of long-standing, insulin-treated type 2 diabetes patients.

Abbreviations: HbA_{1c}, glycosylated hemoglobin; y, year; w, week(s); d, days; DXA, dual X-ray absorptiometry; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy

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Table 1: Body composition, muscle and whole-body oxidative capacity, functional performance and blood plasma analyses

n = 11			
	BEFORE training	**AFTER training**	**P**
BM (kg)	97.5 ± 4.9	97.5 ± 4.8	0.95
WC (cm)	112.6 ± 3.7	113.2 ± 4.0	0.7
Total fat (%)	27.0 ± 0.8	25.9 ± 0.9	0.09
Truncal fat (%)	30.1 ± 1.1	28.8 ± 1.3	0.04
TBLM (kg)	68.9 ± 2.9	69.6 ± 2.7	0.25
LLMM (kg)	20.6 ± 1.0	21.2 ± 0.9	0.03
MRI tot. muscle (cm^3)	3553 ± 173	3653 ± 153	0.08
MRI vast. lat. (cm^3)	499 ± 28	536 ± 81	0.01
Fasting plasma glucose (mmol/l)	10.4 ± 0.9	8.6 ± 0.7	0.05
HbA_{1c} (%)	7.6 ± 0.3	7.2 ± 0.2	0.04
Daily insulin requirement (IU)	92.5 ± 11.1	85.4 ± 12.3	0.26
VO_{2max} (ml/min/kg BM)	24.3 ± 1.4	24.2 ± 1.5	0.87
W_{max} (W/kg BM)	1.6 ± 0.1	1.9 ± 0.2	<0.01
Ave. 1RM	77 ± 4	90 ± 6	<0.01
IMCL (% of water signal)	1.9 ± 0.2	2.0 ± 0.3	0.15
τ_{PCr} (s)	49.4 ± 5.5	45.6 ± 5.6	0.09
τ_{ADP} (s)	22.5 ± 2.9	21.2 ± 2.4	0.43
MAP (mmHg)	105.8 ± 2.3	98.1 ± 3.1	0.02
SP (mmHg)	147.4 ± 3.7	137.9 ± 5.1	0.06
DP (mmHg)	82.5 ± 2.1	78.3 ± 2.4	0.13
Total cholesterol (mmol/l)	4.24 ± 0.17	4.37 ± 0.24	0.55
HDL cholesterol (mmol/l)	0.87 ± 0.07	0.91 ± 0.07	0.55
LDL cholesterol (mmol/l)	3.44 ± 0.13	3.53 ± 0.21	0.57
Triacylglycerol (mmol/l)	2.31 ± 4.26	2.26 ± 3.31	0.86
NEFA (mmol/l)	0.459 ± 0.073	0.367 ± 0.044	0.07
Adiponectin (μg/l)	5.43 ± 0.78	5.47 ± 0.82	0.9
TNF-α (ng/l)	7.19 ± 0.46	7.06 ± 0.47	0.74
hsCRP (mg/l)	2.1 ± 0.6	2.08 ± 0.5	0.4
C-peptide (nmol/l)	0.94 ± 0.14	0.90 ± 0.12	0.7

BM = Body Mass; WC = Waist Circumference; TBLM = Total Body Lean Mass; LLMM = Leg Lean Muscle Mass; MRI tot. muscle and MRI vast. lat. = volume measurements based on MRI data for total upper leg muscle compartment and *M. Vastus Lateralis*, respectively; W_{max} = maximal power output on cycle ergometer; Ave. 1RM = Average weight lifted in 1 Repetition Maximum tests from 5 different resistance exercises; IMCL = intramyocellular lipids; τ_{PCr} = PCr recovery time constant; τ_{ADP} = ADP recovery time constant; MAP = Mean Arterial blood Pressure; SP = mean Systolic blood Pressure; DP = mean Diastolic blood Pressure; NEFA = Non-Esterified Fatty Acids; TNF = Tumor Necrosis Factor; hsCRP = high sensitivity C-reactive Protein