Response of insulin-dependent Type 2 diabetic subjects to a 5-month exercise training program

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Introduction

Insulin resistance is the key player in the pathogenesis and progression of Type 2 diabetes (T2D), leading to a severely impaired blood glucose homeostasis. Intramyocellular lipids (IMCL) have proven to be closely linked to skeletal muscle insulin resistance (reviewed in 1). Recently, also mitochondrial dysfunction has been hypothesised to play a role in the development of skeletal muscle insulin resistance, leading to a reduced ability to oxidize fatty acids and to an accumulation of IMCL (2). Exercise training, in various forms, can influence IMCL, mitochondrial function, as well as insulin sensitivity and has the potential to be an efficient intervention in the prevention as well as the treatment of T2D (3-5).

We studied this triad of IMCL, skeletal muscle mitochondrial function and glucose homeostasis in insulin-dependent T2D patients before and after 5 months of combined strength and endurance exercise training. IMCL levels were measured using single-voxel localized ^{1}H MRS and mitochondrial function was investigated, among other techniques, using ^{31}P MRS.

Materials & Methods

Eleven male T2D patients were selected (mean ± SE: age: 59.1 ± 2.3 years, BMI: 32.2 ± 1.2 kg/m^2). Subjects were diagnosed with T2D over 5 years and were on exogenous insulin treatment for at least 24 months. Patients using thiazolidinediones and/or β-blockers shorter than 6 months, subjects with impaired liver function, renal failure, severe retinopathy or a history of severe cardiovascular problems were excluded from participation.

Subjects participated in a supervised 5-month progressive circuit-training program consisting of 45-60 min of resistance and interval exercises for 3 times a week. All measurements described below were performed before and after the 5-month exercise-training program.

Blood samples were collected after an overnight fast preceded by a standardized meal (35.2 ± 1.8 kJ/per kg body mass). Blood plasma was analysed for plasma glucose and HbA_1c concentration. Maximal whole-body oxygen capacity (VO_{2max}) and maximal workload (P_{max}) were measured during an incremental exercise test until exhaustion on a cycle ergometer using a ramp protocol. Change in body composition was assessed using whole body DEXA (Hologic QDR-4500 Discovery A, Bedford, MA, USA).

Both ^{31}P MRS and ^{1}H MRS of the *M. vastus lateralis* was performed using a 1.5-Tesla whole-body magnet (Gyroscan S15/ACS, Philips Medical Systems, Best, the Netherlands) and spectra were fitted using the nonlinear least squares algorithm AMARES in the jMRUI software package. Single voxel ($10 \times 10 \times 15$ mm^3) localized ^{1}H MR spectra were acquired using the PRESS sequence (TR = 1.5 s, TE = 35 ms, 128 averages and CHESS water suppression), using the body coil for transmission and an 11-cm surface coil for detection. Voxel positions were chosen on scout images, avoiding vascular structures and adipose tissue deposits, and five voxels were measured per subject. Unsuppressed water spectra (32 averages) were recorded from the same voxels and used as an internal reference. ^{31}P MR spectra were acquired using a 6-cm diameter surface coil during a rest-exercise-recovery protocol (repetition time of 3 s, 2 scans/spectrum, time resolution of 6 s). The subjects performed a dynamic single-leg extension exercise with increasing workload resulting in a sufficient phosphocreatine (PCr) depletion without severe muscle acidification. PCr and ADP recoveries were fitted to mono-exponential functions resulting in the metabolites' time constants of recovery, i.e. τ_{PCr} and τ_{ADP}.

Paired student's T-tests were performed to detect differences between data measured before and after the exercise-training program.

Results

The compliance to the exercise-training program was over 85%. Table 1 shows the parameters measured before and after the exercise-training program. Body mass (BM) or waist circumference (WC) of the subjects remained unchanged after 5 months of exercise training. However, whole body fat percentage and fat free leg mass (FFLM) both changed significantly. The blood plasma marker of glucose homeostasis HbA_1c was significantly improved and fasting plasma glucose levels tended to be lower after the exercise-training period. VO_{2max} did not change due to the exercise training, whereas P_{max} increased.

Figure 1 shows examples of typical ^{1}H and ^{31}P MR spectra. ^{1}H MRS measurements revealed no differences between IMCL levels before and after the training program. Also ^{31}P parameters of oxidative capacity, τ_{PCr} and τ_{ADP}, determined from the dynamic ^{31}P MRS measurements showed no improvement due to the exercise training.

Discussion

In these T2D patients suffering from severe muscle deconditoning, the exercise training did result in an improved glucose homeostasis, indicated by the lower HbA_1c and a trend towards lower fasting plasma glucose. This was not accompanied by an amelioration of mitochondrial function (VO_{2max}, τ_{PCr} and τ_{ADP} did not change) or a decrease in IMCL content, both often believed to improve peripheral insulin sensitivity (5). However, as both FFLM and P_{max} did increase, one could argue that muscle function became more efficient due to the exercise program. This was confirmed, albeit in a qualitative way, by the higher workload needed during the ^{31}P-MRS single-leg exercise, to reach similar levels of PCr depletion as before the exercise training (data not shown).

Conclusion

Even in patients with long-term T2D, 5 months of exercise training did result in a modest improvement of glucose homeostasis parameters. This improvement was not accompanied by a lower IMCL content or by an improvement of oxidative capacity, although maximal workload per kg BM did increase. In order to improve mitochondrial function in these patients, the 5-month training program probably needs to be extended with more focus on endurance training, now muscle strength allows for this type of exercise.

References

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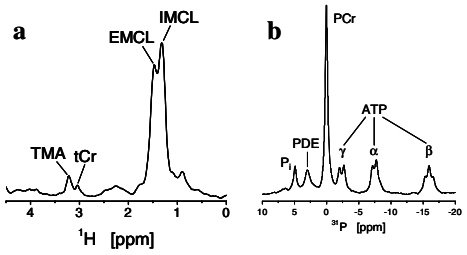

Figure 1. (**a**) Typical ^{1}H MR spectrum (128 averages) and (**b**) ^{31}P MR spectrum (60 averages) at rest, both from the *M. vastus lateralis*

Table 1: Body composition, blood glucose homeostasis, IMCL content and ^{31}P parameters before and after 5 months of exercise training

	BM kg	WC cm	HbA_1c %	Fat %	FFLM kg	Fasting plasma glucose mmol/l	VO_{2max} ml/min/kg	P_{max} Watt/kg BM	IMCL % of water signal	τ_{PCr} s	τ_{ADP} s
PRE training	97.5 ± 4.9	112.6 ± 3.7	7.6 ± 0.3	27.0 ± 0.8	20.6 ± 1.0	10.4 ± 0.9	24.3 ± 1.4	1.6 ± 0.1	2.05 ± 0.28	49.44 ± 5.48	22.47 ± 2.86
POST training	97.5 ± 4.8	113.2 ± 4.0	7.2 ± 0.2	25.9 ± 0.9	21.2 ± 0.9	8.6 ± 0.7	24.2 ± 1.5	1.9 ± 0.2	2.40 ± 0.43	45.56 ± 5.60	21.19 ± 2.45
p-value	0.95	0.69	0.04	0.009	0.033	0.059	0.95	0.0004	0.107	0.088	0.434

BM: body mass, WC: waist circumference, HbA_1c: glycolysated haemoglobin, Fat: whole body fat percentage, FFLM: fat free leg mass, VO_{2max}: maximal oxygen consumption, P_{max}: maximal power output, IMCL: intramyocellular lipid, τ: metabolite's time constant of recovery