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Original article

Training-induced improvement in lipid oxidation in type 2 diabetes mellitus is related to alterations in muscle mitochondrial activity. Effect of endurance training in type 2 diabetes

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Abstract

Aim. – We investigated whether or not, in type 2 diabetic (T2D) patients, an individualized training effect on whole-body lipid oxidation would be associated with changes in muscle oxidative capacity.

Methods. – Eleven T2D patients participated in the study. Whole-body lipid oxidation during exercise was assessed by indirect calorimetry during graded exercise. Blood samples for measuring blood glucose and free fatty acids during exercise, and muscle oxidative capacity measured from skeletal muscle biopsy (mitochondrial respiration and citrate synthase activity), were investigated in the patients before and after a 10-week individualized training program targeted at $LIPOX_{max}$, corresponding to the power at which the highest rate of lipids is oxidized (lipid oxidation at $LIPOX_{max}$).

Results. – Training induced both a shift to a higher-power intensity of $LIPOX_{max}$ ($+9.1 \pm 4.2$ W; $P < 0.05$) and an improvement of lipid oxidation at $LIPOX_{max}$ ($+51.27 \pm 17.93$ mg min^{-1}; $P < 0.05$). The improvement in lipid oxidation was correlated with training-induced improvement in mitochondrial respiration ($r = 0.78$; $P < 0.01$) and citrate synthase activity ($r = 0.63$; $P < 0.05$).

Conclusion. – This study shows that a moderate training protocol targeted at the $LIPOX_{max}$ in T2D patients improves their ability to oxidize lipids during exercise, and that this improvement is associated with enhanced muscle oxidative capacity.

Résumé

L'amélioration de l'oxydation des lipides induite par l'entraînement est liée aux modifications de l'activité mitochondriale musculaire chez des diabétiques de type 2.

Objectif. – Le but de ce travail était d'étudier chez des diabétiques de type 2 (DT2) si les effets d'un entraînement individualisé sur l'oxydation des lipides étaient liés à l'amélioration des capacités oxydatives musculaires.

Méthodes. – Onze diabétiques de type 2 (DT2) ont participé à l'étude. L'oxydation des lipides à l'effort a été évaluée par une calorimétrie indirecte d'effort. Des prélèvements sanguins pour les dosages de la glycémie et des acides gras libres au cours de l'exercice ainsi qu'une biopsie musculaire destinée à étudier les capacités oxydatives musculaires (respiration mitochondriale et activité citrate synthase) étaient réalisés chez les patients avant et après dix semaines d'entraînement individualisé ciblé sur le $LIPOX_{max}$, qui correspond à la puissance à laquelle l'oxydation des lipides est maximale (oxydation des lipides au $LIPOX_{max}$).

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Résultats. – En réponse à l'entraînement, nous avons observé un déplacement du $LIPOX_{max}$ vers des puissances supérieures ($+9,1 \pm 4,2$ W, $P < 0,05$) et une augmentation de l'oxydation des lipides au $LIPOX_{max}$ ($+51,27 \pm 17,93$ mg min^{-1}, $P < 0,05$). L'amélioration de l'oxydation des lipides était corrélée à l'amélioration de la respiration mitochondriale ($r = 0,78$, $P < 0,01$) et à l'amélioration de l'activité citrate synthase ($r = 0,63$, $P < 0,05$) obtenues en réponse à l'entraînement.

Conclusion. – Cette étude montre chez des DT2 qu'un entraînement modéré de faible intensité ciblé sur le $LIPOX_{max}$ améliore l'oxydation des lipides au cours de l'exercice et que cette amélioration est associée à l'amélioration des capacités oxydatives musculaires.

Keywords: Exercise; Insulin-resistance; Mitochondria; Skeletal muscle; Biopsy

Mots clés : Exercice ; Insulinorésistance ; Mitochondrie ; Muscle squelettique ; Biopsie

1. Introduction

The prevalence of type 2 diabetes mellitus (T2D) continues to rise, and a sedentary lifestyle and obesity are recognized as key risk factors. T2D patients are characterized by impaired substrate uptake [1,2]. Using a specific protocol of exercise calorimetry [3–5], we recently reported [6] that the defect in lipid oxidation during exercise in such patients can be described as the balance of substrates used for oxidation during exercise being shifted towards a lower maximum peak of lipid oxidation ($LIPOX_{max}$) and lower exercise-intensity levels.

In addition, in T2D patients, skeletal muscle mitochondrial function appears to be disturbed, leading to, in particular, reduced activity of the electron transport chain [7–9]. However, this mitochondrial dysfunction remains controversial [10]. Nevertheless, it is well established that mitochondria are adaptable organelles directly involved in substrate oxidation, and skeletal muscle can manifest considerable plasticity of mitochondrial activity in response to training in insulin-resistant states, in obese individuals [11] and in T2D patients, as has been recently shown [12]. Interestingly, the defect in lipid oxidation found in both obese and insulin-resistant patients is also highly sensitive to training and, thus, is rapidly corrected by endurance training targeted at the $LIPOX_{max}$ [4,13]. Therefore, it appeared to be logical to extend this approach to people with T2D.

Nevertheless, the mechanism of such training-induced improvement in lipid oxidation remains poorly understood as, to our knowledge, there has been no research into the effect of training on changes in whole-body lipid oxidation and skeletal muscle oxidative capacity in T2D patients.

Thus, the aim of our study was to investigate the effects of a 10-week individualized training program in T2D patients, carried out at the level of the $LIPOX_{max}$ (power intensity at which lipid oxidation is maximum), on whole-body lipid oxidation and skeletal muscle oxidative capacity.

2. Methods

Eleven overweight T2D male patients were enrolled into the study: age (years): 55.4 ± 2.2; height (cm): 177 ± 1.3; weight (kg): 90.9 ± 3.1; body mass index (BMI, kg m^{-2}): 29.0 ± 1.0; fasting blood glucose (mmol L^{-1}): 8.8 ± 1.0; fasting blood insulin (μU mL^{-1}): 10.24 ± 2.18; and HbA_{1c} (%): 7.4 ± 0.4. These patients were all sedentary, with a score less than nine (5.70 ± 1.02) on a questionnaire commonly used for patients with chronic disease [14], and not engaged in any other training programs. All were treated with oral antidiabetic drugs only, and none received insulin or had clinical signs of long-term diabetic complications. All medications were withheld 24 hours before the experiment. Informed consent was obtained from all subjects after explanation of the nature of the study and the risks related to their participation. The study was approved by the local ethics committee (# 03/10/GESE).

3. Experimental design

Each patient visited the laboratory three times at 8 a.m. after an overnight fast. The first visit was for enrollment, and included a clinical examination, a physical-activity questionnaire, anthropometric measurements and obtaining the informed consent. Two days later, the patients returned to the laboratory for an exercise test (see below) and, after a further two days, for a skeletal muscle biopsy of the vastus lateralis. Then, two or three days later, the patients started the training program. At the end of the training, they all underwent a second exercise test and another skeletal muscle biopsy.

4. Exercise testing

The exercise test was performed at 8 a.m. after an overnight fast on an electromagnetically-braked cycle ergometer (550 ERG, Bosch, Germany) that was connected to a breath device (Zan 600, Zan, Germany) to measure gas exchanges (V_{O_2} and V_{CO_2}). The test consisted of five six-minute submaximum steady-state workloads corresponding to 20, 30, 40, 50 and 60% of the maximum theoretical workload ($W_{max\ th}$). This latter figure was calculated according to Wasserman's equation [15]: $[(0.79 \times H - 60.7) \times (50.72 - 0.372 \times A) - 350]/10.3$ if the patient was obese, or $[W \times (50.72 - 0.372 \times A) - 350]/10.3$ if the patient was not obese, where H = height in cm, A = age in years and W = weight in kg.

Blood samples were drawn at rest and during the last minute of each steady-state workload, using a 32-mm catheter placed into a superficial forearm vein, to measure blood glucose and free fatty acids.

Indirect calorimetric measurements were performed to determine whole-body lipid oxidation. V_{O_2} and V_{CO_2} were determined as the mean of the measurements taken during the fifth and sixth minute of each six-minute steady-state work-