Can J Diabetes xxx (2017) 1–8

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Effect of Combined Exercise Versus Aerobic-Only Training on Skeletal Muscle Lipid Metabolism in a Rodent Model of Type1 Diabetes

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Key Messages

- Aerobic exercise training reduces skeletal muscle lipid accumulation in a rodent model of T1D.
- The effects of combined aerobic and resistance training on muscle lipid metabolism in T1D are not well understood.
- Here we report significant improvements in oxidative capacity and skeletal muscle lipid metabolism following combined exercise training in a rodent model of T1D.

ARTICLE INFO

Article history:
Received 26 May 2017
Received in revised form
10 September 2017
Accepted 25 September 2017

Keywords:
aerobic exercise
combined exercise
insulin
resistance exercise
type 1 diabetes

ABSTRACT

Objectives: Abnormal skeletal muscle lipid metabolism is associated with insulin resistance in people with type 1 diabetes. Although lipid metabolism is restored with aerobic exercise training, the risk for postexercise hypoglycemia is increased with this modality. Integrating resistance and aerobic exercise is associated with reduced hypoglycemic risk; however, the effects of this exercise modality on lipid metabolism and insulin resistance remain unknown. We compared the effects of combined (aerobic + resistance) versus aerobic exercise training on oxidative capacity and muscle lipid metabolism in a rat model of type 1 diabetes.
Methods: Male Sprague-Dawley rats were divided into 4 groups: sedentary control (C), sedentary control + diabetes (CD), diabetes + high-intensity aerobic exercise (DAE) and diabetes + combined aerobic and resistance exercise (DARE). Following diabetes induction (20 mg/kg streptozotocin over five days), DAE rats ran for 12 weeks (5 days/week for 1 hour) on a motorized treadmill (27 m/min at a 6-degree grade), and DARE rats alternated daily between running and incremental weighted ladder climbing.
Results: After training, DAE showed reduced muscle CD36 protein content and lipid content compared to CD ($p \leq 0.05$). DAE rats also had significantly increased citrate synthase (CS) activity compared to CD ($p \leq 0.05$). DARE rats showed reduced CD36 protein content compared to CD and increased CS activity compared to CD and DAE rats ($p \leq 0.05$). DARE rats demonstrated increased skeletal muscle lipid staining, elevated lipin-1 protein content and insulin sensitivity ($p \leq 0.05$).
Conclusions: Integration of aerobic and resistance exercise may exert a synergistic effect, producing adaptations characteristic of the "athlete's paradox," including increased capacity to store and oxidize lipids.

Mots clés :
exercice aérobique
entraînement combiné
insuline
exercice contre résistance
diabète de type 1

RÉSUMÉ

Objectifs : L'anomalie du métabolisme lipidique des muscles squelettiques est associée à l'insulinorésistance chez les personnes atteintes du diabète de type 1. Bien que l'exercice aérobique restaure le métabolisme des lipides, cette modalité d'entraînement augmente le risque d'hypoglycémie après l'exercice. L'intégration de l'exercice contre résistance et de l'exercice aérobique est associée à la diminution du risque d'hypoglycémie. Toutefois, on ignore les effets de cette modalité d'entraînement sur le métabolisme des lipides et l'insulinorésistance. Nous avons comparé les effets de l'entraînement combiné (en aérobie+en résistance) par rapport à l'exercice aérobique sur la capacité oxydante et le métabolisme lipidique des muscles dans un modèle de diabète de type 1 chez le rat.

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1499-2671
https://doi.org/10.1016/j.jcjd.2017.09.013

Méthodes : Nous avons divisé des rats Sprague-Dawley mâles en 4 groupes : les témoins sédentaires (T), les témoins sédentaires+diabète (TD), le diabète+l'exercice aérobique à haute intensité (DEA) et le diabète+l'entraînement combiné en aérobie et en résistance (DEAR). Après l'induction du diabète (20 mg/kg de streptozotocine durant cinq jours), les rats DEA ont couru durant 12 semaines (5 jours/semaine durant 1 heure) sur un tapis roulant motorisé (27 m/min à une inclinaison de 6 degrés), et les rats DEAR ont alterné quotidiennement entre la course et la montée d'échelle avec surcharge progressive.
Résultats : Après l'entraînement, les rats DEA ont montré une diminution de la teneur en protéines CD36 et de la teneur en lipides dans les muscles comparativement aux TD ($p \leq 0,05$). Les rats DEA ont également montré une augmentation significative de l'activité du citrate synthétase (CS) comparativement aux rats TD ($p \leq 0,05$). Les rats DEAR ont montré une réduction de la teneur en protéine CD36 comparativement aux rats TD et une augmentation de l'activité du CS comparativement aux rats TD et DEA ($p \leq 0,05$). Les rats DEAR ont démontré une augmentation des taches lipidiques dans les muscles squelettiques, une hausse de la teneur en lipine-1 et une sensibilité à l'insuline ($p \leq 0,05$).
Conclusions : L'intégration de l'exercice aérobique et de l'exercice contre résistance peut exercer un effet synergique, qui produit des adaptations propres au « paradoxe des athlètes », dont l'augmentation de la capacité de stockage et d'oxydation des lipides.

Introduction

Type 1 diabetes results from the autoimmune-mediated destruction of pancreatic beta cells, leading to insufficient insulin secretion and hyperglycemia. Therefore, exogenous insulin therapy is required to maintain normal blood glucose levels. A subset of patients with type 1 diabetes are unable to maintain normal blood glucose levels despite persistent glucose monitoring and insulin adjustment (1). Termed "double diabetes," the combination of immune-related type 1 diabetes and insulin resistance, has been shown to heighten the risk for developing cardiovascular disease (CVD) (2).

Hyperglycemia and abnormal lipid metabolism are believed to initiate the development of insulin resistance in individuals with type 1 diabetes (3). In young, healthy individuals, hyperglycemia increases skeletal muscle lipid accumulation via inhibition of carnitine palmitoyltransferase-1 (CPT-1) which, in turn, reduces mitochondrial beta oxidation (4). Abnormal skeletal muscle lipid metabolism has been shown to stimulate inflammation and the development of insulin resistance, as excess lipid flux through oxidative pathways drives reactive oxygen species (ROS) production and depletes reducing enzymes, such as glutathione (5). Further, the production of harmful lipid species, such as diacylglycerols (DAGs) and ceramides, can exert inhibitory effects on the insulin-signalling pathways (6).

We have previously reported that 10 weeks of aerobic exercise training can ameliorate insulin resistance and improve cardiovascular function in a rodent model of type 1 diabetes (7,8). Regular aerobic exercise training leads to a reduction in the content of insulin-desensitizing lipid intermediates, such as DAG and ceramide (7). Aerobic exercise training also elicits a robust increase in lipid oxidation and the storage of neutral triacylglycerol (TAG), which serves as a source of fatty acid substrate without impairing the insulin-signalling cascade (9–11). Furthermore, aerobic exercise induces significant skeletal muscle adaptations, including mitochondrial biogenesis, increased oxidative capacity (citrate synthase activity) and glucose uptake (12–15), and adenosine monophosphate-activated protein kinase (AMPK) activation during exercise and alleviates CPT-1 inhibition, permitting greater fatty acid transport into the mitochondria for oxidation (16).

Despite the known benefits to metabolic and cardiovascular health, aerobic training remains difficult for patients with type 1 diabetes because there is a significant risk for postexercise hypoglycemia with this modality of exercise. We have previously observed a rapid and significant reduction in blood glucose following acute aerobic exercise in rats with type 1 diabetes, which persists following training (8,17). The American Diabetes Association and Diabetes Canada recommend a combined approach to exercise, involving both aerobic and resistance training for individuals with type 1 diabetes (18). Indeed, it has been shown in individuals with type 1 diabetes that combining resistance with aerobic exercise can attenuate the decline in blood glucose levels evident following aerobic training alone (19). Sustained elevations in catecholamines and/or growth hormone, as a result of resistance training, is believed to enhance hepatic-mediated release of glucose during the subsequent aerobic exercise session (20,21). Among individuals without diabetes, resistance training elicits adaptations different from those of aerobic training, including increased muscle mass and fibre-type conversion (22). Furthermore, resistance training increases mitochondrial function and oxidative capacity as well as insulin sensitivity (23,24).

Little is known regarding the metabolic effects of combined modalities of exercise in patients with type 1 diabetes. In individuals without diabetes, an interference effect has been reported, whereby simultaneously training for strength and endurance hinders strength development and reduces maximum voluntary contraction and running capacity (25,26). In obese individuals and patients with type 2 diabetes, evidence suggests that despite impairments to athletic performance, combined training may significantly improve oxidative capacity, glycemic control, insulin sensitivity and body composition (27–29). Moreover, evidence has shown that the combination of aerobic and resistance exercise is associated with greater improvements in mitochondrial capacity, demonstrated by elevations in citrate synthase activity to a greater extent than either aerobic or resistance training alone in healthy males, as well as in healthy males and females independent of age (27,30,31).

The combination of aerobic and resistance training has been suggested as an effective strategy to mitigate the risk for exercise-mediated hypoglycemia and may provide substantial benefits for cardiovascular and metabolic health (19,32,33). The role of skeletal muscle lipid metabolites in the development of insulin resistance has been established in obese populations and in those with type 2 diabetes, but their association with insulin resistance in type 1 diabetes remains unclear (34,35). Work is needed to better understand the effects of exercise on muscle lipid metabolites in type 1 diabetes, particularly combined exercise, because it may be a safer modality for this population. The purpose of this study was to determine whether combined (aerobic and resistance) exercise is an effective means of improving skeletal muscle oxidative capacity and lipid metabolism. We hypothesized that combined exercise training would reduce intramyocellular lipid and enhance oxidative capacity in skeletal muscle of rodents with type 1 diabetes to an equal or greater extent than aerobic training alone.

Methods

Ethics approval and animals

Eight-week-old male Sprague-Dawley rats were obtained from Charles River Laboratories (St. Constant, Quebec) and housed 2 per