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EFFECTS OF EXERCISE TRAINING ON REGULATION OF SKELETAL MUSCLE GLUCOSE METABOLISM.

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Abstract:

The aim was to investigate the molecular mechanisms behind exercise traininginduced improvements in glucose regulation in aged subjects. Twelve elderly male subjects completed 8 weeks of exercise training. Before and after the training period, the subjects completed an oral glucose tolerance test (OGTT) and a muscle biopsy was obtained from the vastus lateralis before and 45 minutes into the OGTT. Blood samples were collected before and up to 120 minutes after glucose intake. The present results suggest that exercise training improves glucose regulation in elderly subjects by enhancing the capacity and acute regulation of glucose uptake and by enhancing intracellular glucose removal to glycogen synthesis rather than glucose oxidation.

Keywords: *Physical activity—Aging—Pyruvate dehydrogenase—Glycogen synthase—Insulin signaling.*

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INTRODUCTION:

Aging is associated with impaired glucose metabolism as demonstrated both by reduced glucose tolerance during an oral glucose tolerance test [OGTT] and reduced glucose disposal during a hyperinsulinemic glycemic clamp (1)(2). Such changes may pre-dispose to diseases like type 2 diabetes and prevention of age-related dysfunctional glucose metabolism through physical activity is therefore important (3). Regular physical activity has been shown to increase glucose tolerance and insulin sensitivity in elderly subjects to a similar extent as in young subjects (4). Aging and exercise training associated changes in glucose tolerance and insulin sensitivity involve several tissues, but changes in skeletal muscle metabolism have a particularly large impact on whole body metabolism (5). Glucose 6 phosphate (G-6-P) will in a resting muscle cell either be incorporated into glycogen or be oxidized within the mitochondria. The rate limiting enzyme in glycogen formation is glycogen synthase (GS), while the pyruvate dehydrogenase (PDH) complex converts pyruvate to acetyl CoA in an irreversible step, which represents the only entry of carbohydrate-derived substrates into the mitochondria for oxidation (6). GS is stimulated allosterically by G-6-P and inactivated by phosphorylation (7). Insulin is known to increase the activity of GS through insulin-stimulated activation of Akt and concomitant phosphorylation and inactivation of GSK3 (8). Activity of PDH in the active form (PDHa) is primarily determined by the phosphorylation level of the PDH-E1α subunit regulated by PDH kinases (PDK), which phosphorylate and inactivate PDH, and PDH phosphatases (PDP), which dephosphorylate and activate PDH (9). PDHa activity has previously been shown to increase in human skeletal muscle in response to oral glucose intake, and to either increase or remain unchanged during a hyperinsulinemic euglycemic clamp in humans. In accordance with an insulin-mediated regulation of PDHa activity, insulin has been reported to increase PDP activity and to reduce PDK4 protein in rat skeletal muscle (10,11, 12). Previous studies have observed either reduced or unchanged GLUT4 protein content in human skeletal muscle with increasing age (13). Moreover, the recent finding that aging was associated with impaired insulin-induced TBC1D4 phosphorylation in skeletal muscle suggests that reduced insulin-mediated GLUT4 translocation may contribute to insulin resistance in aged subjects. Furthermore, skeletal muscle HKII activity has been shown to be lower in elderly than in young subjects indicating that a reduced ability to maintain the transmembrane glucose gradient also may affect skeletal muscle glucose uptake in aged subjects (14). Knowledge about potential age-related effects on GS and PDH regulation in skeletal muscle is scarce. However, total GS activity has been reported to be reduced with age (15). Moreover, insulin-stimulated GS activation has been demonstrated to be impaired in Type 2 diabetes (T2D) patients (16). Similarly, an insulin-induced increase in PDHa activity has been reported to be abolished in T2D patients (17). In line with this observation, T2D has been shown to be associated with impaired insulin-mediated down-regulation of PDK4 in skeletal muscle suggesting that PDK4-induced inhibition of PDH and hence inhibition of glucose oxidation may contribute to insulin resistance (18). Together, this indicates that both oxidative and nonoxidative glucose removal are reduced in skeletal muscle of T2D patients. This may suggest that GS and PDH dysregulation also contributes to ageassociated glucose intolerance and insulin resistance (19). Exercise training has previously been shown to increase skeletal muscle protein content of GLUT4, HKII, Akt, TBC1D4, GS, PDK2, and PDH-E1α in young subjects and similarly for GLUT4 and Akt2, but not TBC1D4 in elderly subjects (20). Furthermore, exercise training has been demonstrated to enhance insulin-mediated TBC1D4 and GS regulation in skeletal muscle of young subjects as well as to reverse the age-associated impairment of insulin-stimulated TBC1D4 phosphorylation in skeletal muscle (21). Therefore, the purpose of the present study was to test the hypotheses that exercise training-induced improvements in whole body glucose metabolism in elderly men are associated with increased content of key factors involved in GS and PDH regulation in skeletal muscle, and enhanced acute regulation of GS and PDH in skeletal muscle upon glucose intake.

METHODS:

Twelve physically inactive but healthy male subjects, 60–72 years of age with an average body mass index of 26.0±0.5kg/m2 participated in the study. Initially 13 subjects were included but one of the subjects did not complete the current protocol described below. All subjects were nonsmokers and underwent a medical examination. None had been diagnosed with cardiovascular disease, hypertension, renal dysfunction, insulin resistance or type 2 diabetes, and all subjects had normal ECG. One subject was diagnosed with hypercholesterolemia regulated by his own physician (medication was maintained during the experimental period). The other participants had normal cholesterol levels. The subjects exercise trained for 8 weeks, 4 days a week. The training was a combination of supervised high intensity cycling exercise (spinning) on cycle ergometers performed two times per week, strength and mobility training

(crossfit) once per week and a 5 km walk once a week . Before and after the intervention period, the subjects were challenged with an OGTT (1g/kg body mass). A muscle biopsy was obtained from vastus lateralis before and 45 minutes after glucose intake using the Bergström needle biopsy method with suction. Blood samples were obtained before and up to 2 hours after glucose intake. After the training period, the OGTT was performed ~48 hours after the last exercise. Statistics Values are presented as mean ± SE. A student paired t-test was used to test the effect of exercise training on fasting plasma insulin and glucose as well as skeletal muscle protein content. Two-way ANOVA with repeated measures was used to test the effect of exercise training and glucose intake on plasma glucose, insulin and c-peptide as well as skeletal muscle protein and protein phosphorylation levels. When a main effect was observed, a Student–Newman–Keuls post hoc test was used to locate differences between groups. The data set was log transformed if the results did not pass the equal variance test. Fasting plasma insulin and plasma glucose concentrations were not different before and after the 8 weeks of exercise training. The plasma glucose response during the OGTT was similar in the untrained and trained state increasing ($p < .05$) in both conditions to approximately 8mM 30 minutes after glucose intake and returning to the basal level (~5mM) at 120 minutes after intake. There was no difference in the plasma glucose concentration between the untrained and the trained state. The plasma insulin concentration increased ($p < 0.05$) 120 minutes after intake relative to before both in the untrained and trained state. Moreover, the plasma insulin concentration was at 15 minutes after glucose intake higher ($p < .05$) and at 90 and 120 minutes lower ($p < .05$) in the trained than in the untrained state. The plasma C-peptide concentration increased ($p < .05$) at 120 minutes relative to before intake. Moreover, as for the plasma insulin concentration, the C-peptide concentration was at 90 and 120 minutes after glucose intake lower ($p < .05$) in the trained than in the untrained state. The C-peptide AUC was ~15% lower ($p < .05$) after exercise training than before. Muscle glycogen The muscle glycogen concentration increased ($p < .05$) and HKII ($.05 \leq p < .1$) increased 1.2- to 1.8-fold with exercise training. There was no difference in Akt1, TBC1D4, GSK-3β, or PDK4 protein content before and after exercise training. Intracellular Signaling Akt phosphorylation Forty-five minutes after glucose intake, the absolute Akt Thr308 phosphorylation increased ($p < .05$) 2.8- and 3.7-fold relative to before glucose intake in the untrained and trained skeletal muscle, respectively, with no difference between training status. The absolute phosphorylation on Akt Ser473 increased ($p < .05$) 2.1- and 3-fold in response to glucose intake in the untrained and trained state, respectively, reaching a 2-fold higher ($p < .05$) level in the trained than untrained state TBC1D4 phosphorylation The absolute TBC1D4 Thr642 phosphorylation in skeletal muscle increased ($p < .05$) 1.8-fold in the untrained state and 2.5-fold in the trained state in response to glucose intake reaching a 1.2-fold higher ($p < .05$) level in the trained than the untrained state. GSK3β phosphorylation Absolute GSK3β Ser9 phosphorylation in skeletal muscle increased ($p < .05$) similarly 1.3- to 1.4-fold 45 minutes after glucose intake relative to before both before and after the exercise training period with no difference between the two conditions. GS Regulation GS site 2±2a Glucose intake had no effect on the absolute GS site 2 + 2a phosphorylation in skeletal muscle before exercise training, but after exercise training the absolute GS site 2 + 2a phosphorylation decreased ($p < .05$) 20% in response to glucose intake. Furthermore, the absolute GS site 2 + 2a phosphorylation was in the trained state 1.4-fold higher ($p < .05$) in the basal state and tended to be 1.2-fold higher ($.05 \leq p < .1$) 45 minutes after glucose intake than in the untrained state. GS site 3a The absolute GS site 3a phosphorylation in skeletal muscle tended to decrease ($.05 \leq p < .1$) 25% in response to glucose intake before exercise training and decreased ($p < .05$) 40% with glucose intake after exercise training. The absolute GS site 3a phosphorylation was 1.3- to 1.7-fold higher ($p < .05$) in the trained state than in the untrained state. GS activity The GS activity (I-form) in skeletal muscle did not change with glucose intake before exercise training, but increased ($p < .05$) 1.3-fold 45 minutes after glucose intake in the exercise-trained state. There was no difference in GS activity between the untrained and trained state. PDH Regulation PDH phosphorylation There was no effect of glucose intake on the absolute PDH site 1 and site 2 phosphorylation in skeletal muscle. Exercise training increased ($p < .05$) the absolute phosphorylation level of both sites with 1.3- to 1.8-fold, but this effect was removed by normalization to PDH-E1α protein, except for site 2 phosphorylation in the basal state PDHa activity There was no effect of glucose intake on skeletal muscle PDHa activity before exercise training, but glucose intake decreased ($p < .05$) the PDHa activity 30% after the exercise training period. PDK4 Protein PDK4 protein content in skeletal muscle overall (untrained and trained state together) tended to be lower ($.05 \leq p < .1$) after glucose intake than before.

\DISCUSSION:

The main findings of the present study are that exercise training improved whole body glucose regulation in elderly healthy subjects was associated with increased skeletal muscle HKII, GLUT4, Akt2, PDK2, GS, and PDH-E1α protein content. Moreover, exercise training resulted in an enhanced response of TBC1D4 and GS and a reduced PDHa activity in skeletal muscle after glucose intake relative to before training. The present observation that the plasma glucose response to an oral glucose intake was similar before and after the exercise training period shows that glucose tolerance was unaffected by the exercise training intervention. However, the lower insulin and C-peptide plasma concentrations as well as the lower AUC for insulin and C-peptide during the OGTT after training than before training indicate that exercise training improved the insulin sensitivity in the present study. This is further supported by the higher Matsuda index after exercise training than before in the current study. Such an exercise training effect is in line with the observations in previous studies using hyperinsulinemic euglycemic clamp in elderly subjects demonstrating enhanced whole body insulin action as well as improved insulin sensitivity in skeletal muscle after exercise training. The finding in the current study that glucose intake induced a more marked absolute TBC1D4 phosphorylation after exercise training than before is in accordance with a recent study demonstrating that insulin-stimulated TBC1D4 phosphorylation during a hyperinsulinemic euglycemic clamp was higher after a training period than before in aged subjects (22). This indicates that exercise Together these observations suggest that increased capacity for glucose transport and phosphorylation as well as acute regulation of glucose uptake in skeletal muscle will contribute to exercise training-induced improved regulation of skeletal muscle glucose uptake in elderly subjects. The observation that glucose intake did not affect GS activity in the elderly subjects in the untrained state is in contrast with previous observations in young subjects suggesting an age-associated impairment in GS regulation (23). However, the finding that glucose intake induced an increase in GS activity in the elderly subjects after the exercise training period in the present study may indicate that exercise training restored the ability of the aged muscle to activate GS in response to glucose intake. This is in accordance with a previous study reporting improved nonoxidative glucose metabolism in elderly subjects after a training period (24). The finding that PDHa activity was unaffected by the glucose intake in the untrained state is not in accordance with the previously reported increase in PDHa activity in young subjects during an OGTT (25). While a hyperinsulinemic euglycemic clamp is seen as the golden standard in investigating insulin-stimulated glucose regulation and can provide highly important information, it is also an un-physiological situation. The OGGT was therefore used in the current study to reflect glucose metabolism during a physiological setting with an endogenous insulin response to a standard glucose load. Furthermore, the present findings that exercise training induced adaptations in several metabolic parameters underline that aged skeletal muscle can adapt to exercise training. However, it should be mentioned that the subjects were healthy elderly men and whether similar effects will be present in healthy elderly women or T2D patients remain to be determined.

CONCLUSION:

The present findings suggest that exercise training improved glucose regulation in elderly subjects is associated with enhanced potential for GLUT4 translocation, glucose phosphorylation and intracellular glucose removal to glycogen synthesis rather than oxidation.

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