Journal of Traditional and Complementary Medicine 7 (2017) 141–144

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Original article

Improving glucose tolerance by muscle-damaging exercise

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ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form
5 January 2016
Accepted 27 February 2016
Available online 7 May 2016

Keywords:
Muscle damage
Eccentric exercise
Creatine kinase
Blood glucose

ABSTRACT

Tissue damage is regarded as an unwanted medical condition to be avoided. However, introducing tolerable tissue damages has been used as a therapeutic intervention in traditional and complementary medicine to cure discomfort and illness. Eccentric exercise is known to cause significant necrosis and insulin resistance of skeletal muscle. The purpose of this study was to determine the magnitude of muscle damage and blood glucose responses during an oral glucose tolerance test (OGTT) after eccentric training in 21 young participants. They were challenged by 5 times of 100-meter downhill sprinting and 20 times of squats training at 30 pounds weight load for 3 days, which resulted in a wide spectrum of muscle creatine kinase (CK) surges in plasma, 48 h after the last bout of exercise. Participants were then divided into two groups according the magnitude of CK increases (low CK: +48% ± 0.3; high CK: +137% ± 0.5, $P < 0.05$). Both groups show comparable decreases in blood glucose levels in OGTT, suggesting that this muscle-damaging exercise does not appear to decrease but rather improve glycemic control in men. Conclusion: The result of the study rejects the hypothesis that eccentric exercise decreases glucose tolerance. Improved glucose tolerance with CK increase implicates a beneficial effect of replacing metabolically weaker muscle fibers by eccentric exercise in Darwinian natural selection fashion.

1. Introduction

Moderate traumatic physical challenge has been frequently used as a therapeutic modality in traditional Chinese medicine,[1] which leads to an anticipation of beneficial health outcome following muscle-damaging exercise.[2] We have previously reported an increased necrosis and white blood cell infiltration in exercised muscle after downhill running, an exercise regimen containing eccentric muscle contraction.[3] However, decreased insulin sensitivity in glucose transport and impaired glycogen storage of skeletal muscle after eccentric muscle contraction has been reported in animals and humans.[4,5]

Skeletal muscle, accounted for 40% of body weight, is the major tissue for post-meal glucose uptake. Approximately 85% of postprandial glucose in circulation is disposed into muscle tissues.[2] The whole-body insulin sensitivity, assessed by hyperinsulinemic euglycemic clamp technique, suggests that insulin resistance occurs during the first 48 h after eccentric exercise.[6,7] Decreased muscle insulin sensitivity is expected to produce a negative consequence in the whole-body glycemic regulation. Based on these findings, we hypothesized that muscle-damaging exercise training will decrease glucose tolerance in men. Blood creatine kinase (CK) level has been commonly used to measure the levels of exercise-induced muscle damage. Histological analysis suggests that blood level of muscle CK should be regarded as a biomarker for post-exercise muscle regeneration.[2,8] In this study, we assessed oral glucose tolerance together with muscle CK in plasma, two days following the last bout of exercise training containing eccentric muscle contraction. We tested the hypothesis that 1) muscle-damaging exercise will decrease the whole-body glucose tolerance; 2) The degree of CK increase is associated with attenuated glucose tolerance in men.

2. Methods

2.1. Participants

Twenty-one healthy junior athletes (16.3 ± 0.5 years of age) with no history of musculoskeletal disorders of the lower limbs

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

http://dx.doi.org/10.1016/j.jtcme.2016.02.004

were enrolled in this study. All participants were requested to avoid physical training and medication during the experimental period. Participants provided informed consent prior to participation in the study. This study was conducted in accordance with the guidelines in the Declaration of Helsinki.

2.2. Experimental procedure

Participants performed barbell front squat and downhill run for 3 consecutive days then allowed to rest for another 2 days (Fig. 1). This physical challenge produced a wide range of muscle damage among participants. For OGTT, blood was collected at Day 1 before exercise challenge and again at Day 4, 12 h after the last bout of training. To verify the result of muscle damage, blood sample was collected at Day 1 (24 h) and day 2 (48 h) for CK analysis after the last exercise bout.

2.3. Muscle-damaging exercise

2.3.1. Barbell front squat

Participants were instructed to perform 5 sets of barbell front squat for 20 repetitions at 30 pounds a day for 3 consecutive days and allowed to rest for another 3 consecutive days.

2.3.2. Downhill sprinting

The 100-meter downhill sprinting consisted of 5 repetitions a day for 3 consecutive days and allowed to rest for another 3 consecutive days.

2.4. OGTT

Under a 12-h overnight fasted condition, a 500-ml solution containing 75 g of glucose was orally delivered, and blood was taken from the finger at 0 (before the solution load), 30, 60 and 90 min afterward. Blood glucose level was determined by an automated glucose analyzer (LifeScan, Inc., Milpitas, California 95035, USA).

2.5. Plasma creatine kinase (CK) analysis

CK (CKMB isoform) in plasma is an indicator of muscle regeneration after exercise-induced muscle damage. Plasma sample was taken from fingertip to measure muscle CK activity. Plasma was obtained by centrifuging the blood at 4 °C for 10 min at 3000 rpm and was stored at −80 °C until analysis. CK activity was measured using a DT-60 automated hematology analyzer (Kodak Co., Rochester, NY, USA).

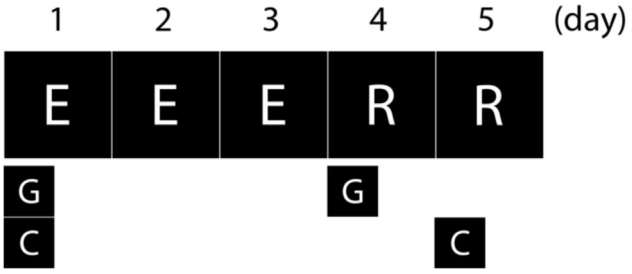

Fig. 1. Time table of experimental procedure. Participants were scheduled to be challenged by eccentric exercise for 3 consecutive days from Day 1 to Day 3, then allowed to recover for another 2 days (from Day 4 and Day 5). Prior to the exercise, oral glucose tolerance test (OGTT) and creatine kinase (CK) measurements were carried out to obtain basal values. OGTT was conducted again 24 h after the last exercise at day 3 and CK was measured again at the end of day 5. E, eccentric exercise; R, rest (no exercise); G, OGTT measurement; C: CK measurement.

2.6. Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical differences between groups were calculated by analysis of variance (ANOVA). Student's t-test was used to compare the mean difference in each variable between the two groups (low CK group vs. high CK group). Statistical significance for type I error was set at $P < 0.05$ for all measures.

3. Results

The current exercise challenge protocol (Fig. 1) results in a wide range of muscle CK surge (Table 1). For those participants showing relatively lower CK increases (Fig. 2A), glucose levels during OGTT decreased significantly after exercise, indicating an improvement in the glucose tolerance. However, for those participants showing relatively high CK increase (Fig. 2B), similar magnitude of improvement on glucose level during OGTT was also reached. Data on area under curve (AUC) in OGTT show no difference in improvement of glycemic control between two groups (Fig. 2C).

4. Discussion

It has been shown that aerobic endurance exercise, as an exercise regimen producing insignificant muscle damage, can improve glucose tolerance.[9] On the other hand, muscle-damaging eccentric muscle contraction results in insulin resistance in glucose transport and glycogen storage of exercised skeletal muscle.[4,5] Based on these early findings, we hypothesized that muscle-damaging exercise will decrease glucose tolerance in humans. However, the result of the study rejects our hypothesis. In a contrary, our data suggest the benefit of improving glycemic control by a muscle-damaging exercise.

Skeletal muscle is the main storage site of postprandial glucose after a carbohydrate meal.[2] Therefore, insulin sensitivity of skeletal muscle should significantly influence the whole-body glucose tolerance. The previous report on onset of muscle insulin resistance after eccentric muscle contraction appears to be associated with

Table 1
Plasma levels of muscle creatine kinase.

Unit: U/L	PRE	Post	% Increase
A	292	313	7%
B	668	726	9%
C	479	618	29%
D	391	526	35%
E	379	521	37%
F	232	376	62%
G	283	476	68%
H	242	416	72%
I	240	416	73%
J	200	372	86%
K	229	427	86%
L	223	426	91%
M	222	432	95%
N	275	536	95%
O	182	364	100%
P	231	482	109%
Q	80	178	123%
R	117	326	179%
S	128	368	188%
T	90	275	206%
U	109	364	234%
Mean	252	426	94%

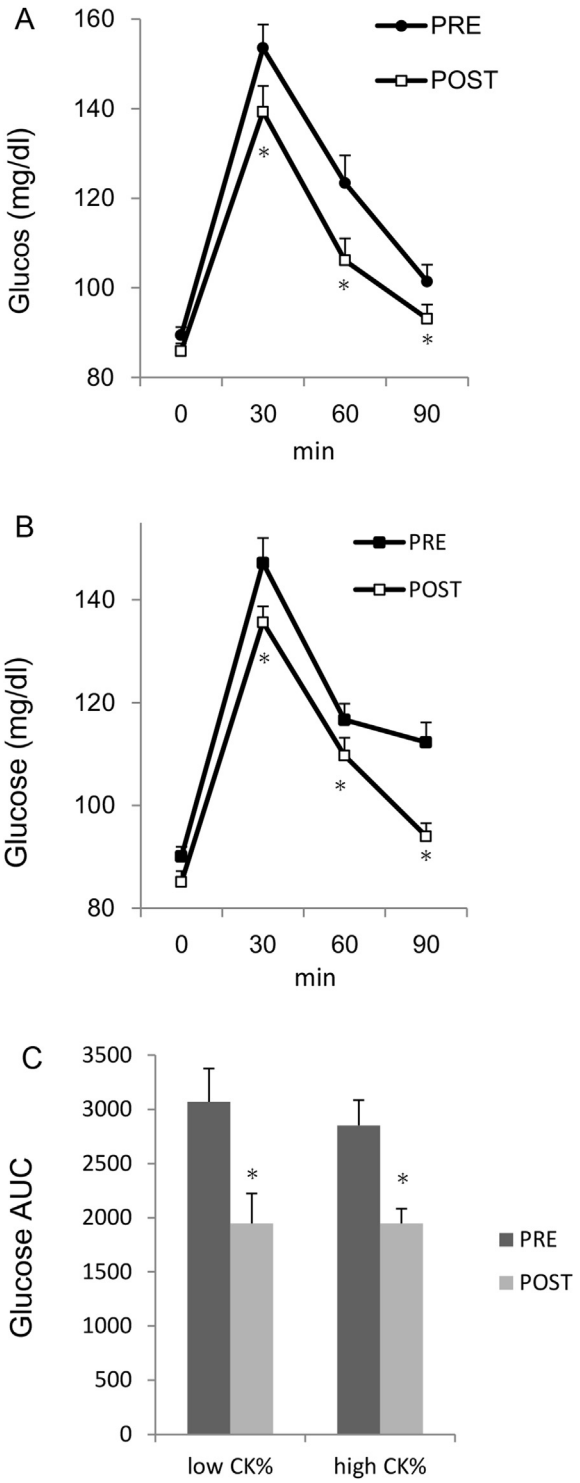

Fig. 2. Oral glucose tolerance test (OGTT). Blood glucose levels decreased to a similar extent for both the halves with lowest CK increases (A) and the halves with highest CK increases (B). Area under curve (AUC) of glucose levels are shown in (C). Pre: Before exercise challenge; Post: After exercise challenge. *Significantly different against Pre, $P < 0.05$.

decreases in glucose transporter GLUT4 protein in skeletal muscle.[4–6] One possibility to explain this discrepancy may be associated with the time after the first bout of exercise challenge. In the current study, our participants conducted 3-day downhill running and measurements were conducted 2 days after the last bout of exercise. Glycemic condition may be changing overtime during different stage of the post-exercise recovery. In addition, it has been reported that a single bout of eccentric exercise can result in an increased insulin secretion in response to hyperglycemia.[10] This is based on results from a hyperglycemic clamp assessment, which shows an initial elevation in insulin release at the first 10 min of glucose infusion. Our current data show decreased blood glucose during OGTT, suggesting that either insulin sensitivity or increased insulin secretion must take place to lower blood glucose levels. Therefore, the result of lower glucose response in OGTT after the muscle damaging exercise is likely associated with concurrent increased response of insulin secretion from pancreatic beta cells and improved insulin sensitivity of exercised muscle.

In this study, all participants were challenged with the same exercise protocol. A wide spectrum of muscle damage was produced among different participants. Based on our hypothesis, if muscle damage can lower insulin sensitivity, we should observe differences in OGTT response between high CK and low CK group. However, our results failed to show proportionality between CK change and OGTT improvement. They are reaching similar levels of low glucose following training. The most likely explanation is that the exercise challenge damaged relatively weaker muscle fiber with insufficient metabolic function. It is quite easy to perceive that healthy muscle fibers have greater chance of survival after an entropic challenge. There may be a great variation in the proportion of unhealthy versus healthy muscle fibers among participants due to individual's variation in training status or lifestyle. Thus the exercise challenge lowers the unhealthy population of muscle fibers of all participants to a similar level, regardless their pre-existing percentage of metabolically weaker muscle fibers. Human body may be considered as a society composed by cells, where the principle of Darwinian natural selection should apply. It has been shown that all-cause mortality decreases as exercise intensity increases,[11,12] suggesting that removing relatively less robust cells in human body by greater challenge can bring more beneficial outcome. We speculate that enhance muscle fiber renewal may be the most important mechanism accounted for the beneficial outcome of the entropic challenge in glycemic control. Skeletal muscle cells in human body are relatively short-lived compared to brain[13] and is continuously dying and regenerating overtime.[14] During early stage of muscle development, GLUT1 protein (low Km transporter) is predominantly expressed followed by increasing GLUT4 expression as muscle mature. Thus, younger muscle fibers offer a greater permeability to plasma glucose across sarcolemma.[15]

Limitation of the study is the young age of the participants. Therefore, the knowledge generalized from the study for older population deserves more experimental confirmation. It is generally known that the individuals having greater needs for better glycemic control are those middle-aged or elderly people. Therefore, the current result does not provide direct answer with regard to whether muscle-damaging exercise is able to improve glucose tolerance at higher age level.

In conclusion, according to previous finding on decreased insulin sensitivity of skeletal muscle after eccentric muscle damaging exercise, we hypothesized that downhill running with resistance exercise will result in deterioration in OGTT. However, the present results reject our hypothesis. In a contrary, muscle damaging exercise effectively improves glucose tolerance independent of CK surge. This finding implicates that metabolically weaker muscle fibers are replaced by newly generated cell population after muscle-damaging eccentric exercise.

Conflict of interest

None declared.

Acknowledgments

We would like to thank generous supports from Ministry of Science and Technology and University of Taipei, Taiwan.

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