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Letter to the Editor

Effects of Different Exercise Modes and Intensities on Skeletal Muscle Mammalian Target of Rapamycin Signaling in Streptozotocin and High-Fat-Diet Induced Prediabetic Mice

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Dear Editor-in-Chief

One of the notable characteristics of diabetes is atrophy of skeletal muscle fibers, which is a result of increased proteolysis, decreased protein synthesis, and decreased regenerative ability of damaged skeletal muscle (1,2). In diabetes, skeletal muscles show decreased expression of mammalian target of rapamycin (mTOR), involved in the process of muscle fiber growth and regeneration through muscle fiber and cell proliferation and differentiation, suggesting that the decreased function of mTOR can induce muscle fiber damage and dissolution due to suppression of muscle fiber proliferation and differentiation (2,3). Diabetes-induced rats through 3-day streptozotocin (STZ) treatment showed decreased protein synthesis within skeletal muscles to 60% and decreased mTOR expression to 36%, proving that skeletal muscle atrophy in diabetes stems from decreased mTOR expression (1).

On the other hand, exercise induces upregulation of mTOR expression, resulting in the growth and hypertrophy of skeletal muscle fibers, as well as having a positive role in glucose kinetics and metabolic status improvement, showing that it can suppress the atrophy of muscle fibers that occurs in diabetes (2,3).

Although the atrophy of skeletal muscles can start at the prediabetic stage, such as impaired glucose tolerance and/or impaired fasting glucose (4), no study has examined the changes in mTOR expression according to exercise in a prediabetes model. Thus, this study aimed to investigate the effect of different types and intensity of exercise on mTOR signaling in skeletal muscles by analyzing mTOR, mTORC1, which is a main regulator of protein synthesis and cell growth, and mTORC2, which is a regulator of glucose absorption and activation of protein kinase B, in prediabetic mice induced by STZ and high-fat-diet.

The experimental animals included 48 C57BL/6 mice (aged 32 weeks) divided into control (CON, n=8) and prediabetes-induced (n=40) groups. The CON group consumed general diet (fat 6.3%) for 4 weeks. On the other hand, the prediabetes-induced group consumed high-fat diet (fat 45%) for 4 weeks; prediabetes was induced at 36 weeks of age by injecting twice in the lower abdomen a 40 mg/kg solution that was made by dissolving STZ (Sigma Chemical, USA) in 0.1 M sodium citrate solution (pH 4.5), after fasting the mice for 6 hours. The mice with a fasting glucose level of 180~250 mg/dL were defined as prediabetes. Thirty-seven-week mice that were identified as having prediabetes were randomly assigned to a prediabetes group that did not participate in the exercise program (PD, n=8), a PD+moderate-intensity endurance exercise

group (PDME), a PD+high-intensity endurance exercise group (PDHE), a PD+moderate-intensity resistance exercise group (PDMR), and a PD+high-intensity resistance exercise group (PDHR). The PDME and PDHE groups performed a treadmill running exercise 5 days a week, for 40 minutes a day, while the PDMR and PDHR groups did a ladder-climbing exercise 5 days a week for 8 weeks (Table 1).

Table 1: Exercise protocols of the study groups

Group	*Duration (week)*	*Speed (m/min)*	*Time (min)*
PDME	1~4	5	5
		8	30
		5	5
	5~8	5	5
		8	10
		10	20
		5	5
PDHE	1~4	5	5
		12	30
		5	5
	5~8	5	5
		12	10
		14	20
		5	5
Group	***Weight (kg)***	***Repetition (set)***	***Grade (°)***
PDMR	50% 1-RM	8	80°
PDHE	75% 1-RM	8	80°

PD, prediabetes group; PDME, PD+moderate-intensity endurance exercise group, PDHE, PD+high-intensity endurance exercise group; PDMR, PD+moderate-intensity resistance exercise group; PDHR, PD+high-intensity resistance exercise group; 1-RM, one repetition maximum

The expressions of mTOR, mTORC1, and mTORC2 in skeletal muscle were analyzed by the Western blot method using antibodies #2972 (CST, USA), #2280 (CST, USA), and #2114 (CST, USA), respectively.

The data of this study were expressed as mean and standard error. They were analyzed using SPSS windows version 25.0 software (SPSS Inc., USA); one-way analysis of variance was conducted to examine group differences. All statistical significance was set at $P<0.05$.

Change of mTOR, mTORC1, and mTORC2 expressions in skeletal muscle induced by different exercise types and intensity are shown in Fig. 1. Statistical analysis showed that the mTOR expression level in skeletal muscle was significantly higher in the PDHE and PDHR groups than in the PD group ($P<0.05$). Moreover, mTORC1 and mTORC2 expression levels were significantly higher in the PDHR group than in the PD group ($P<0.05$).

Putting together the above results, mTOR activation can be dependent on exercise intensity, and resistance exercise can induce relatively higher activation compared with endurance exercise.

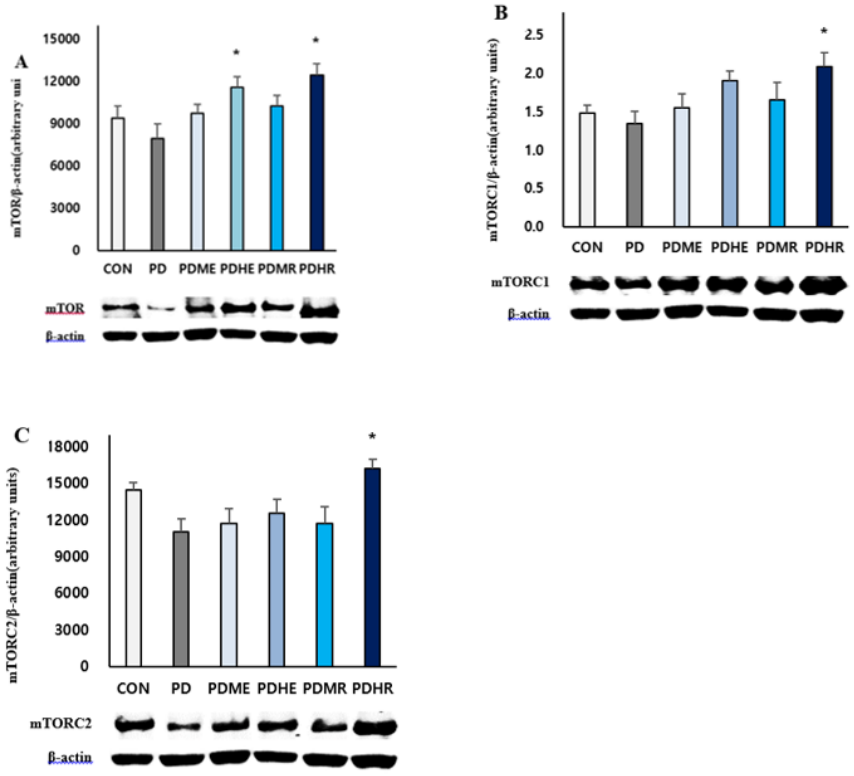

Fig. 1: Change in mTOR (A), mTORC1 (B), mTORC2 (C) expression in skeletal muscle induced by different exercise types and intensity.
Data are presented as mean ± standard error
CON, control group; PD, prediabetes group; PDME, PD+moderate-intensity endurance exercise group, PDHE, PD+high-intensity endurance exercise group; PDMR, PD+moderate-intensity resistance exercise group; PDHR, PD+high-intensity resistance exercise group

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Conflict of interests

The authors declare that there is no conflict of interests.

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