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EFFECT OF EXERCISE TRAINING OF DIFFERENT INTENSITIES ON ANTI-INFLAMMATORY REACTION IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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ABSTRACT: The study investigated the effect of high- and low-intensity exercise training on inflammatory reaction of blood and skeletal muscle in streptozotocin (STZ)-induced diabetic male Sprague-Dawley rats (243 ± 7 g, 8 weeks). The rats completed treadmill running in either high-intensity exercise (6 weeks of exercise training, acute bouts of exercise) or low-intensity exercise (6 weeks of exercise training). Non-running, sedentary rats served as controls. To induce diabetes mellitus, rats received a peritoneal injection of STZ (50 mg · kg^{-1}). Rats were sacrificed immediately after an acute bout of exercise and 6 weeks of exercise training. Inflammatory factors were analyzed by ELISA and by immune blotting from the soleus and extensor digitorum longus muscles. In the serum, inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-4) and reactive oxygen species (ROS) (nitric oxide and malondialdehyde) increased in diabetic rats. However, all exercise training groups displayed reduced inflammatory cytokines and reactive oxygen species. In skeletal muscles, low-intensity exercise training, but not high intensity exercise, reduced the levels of COX-2, iNOS, and MMP-2, which were otherwise markedly elevated in the presence of STZ. Moreover, the levels of GLUT-4 and MyoD were effectively increased by different exercise intensity and exercise duration. Low-intensity exercise training appeared most effective to reduce diabetes-related inflammation. However, high-intensity training also reduced inflammatory factors in tissue-specific muscles. The data implicate regular exercise in protecting against chronic inflammatory diseases, such as diabetes.

KEY WORDS: diabetes mellitus, intensity exercise training, inflammation, ROS, GLUT-4, MyoD

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycaemia resulting from defects of insulin secretion or insulin resistance. The inflammatory process is important in the pathogenesis of diseases including DM [1,9]. Increased levels of inflammatory mediators have been reported in diabetes as a consequence of hyperglycaemia [5]. The chronic complications of DM including damage to blood vessels and nerves result in muscle weakness and muscle atrophy [28]. Therefore, the genesis and progression of diabetes occur due to the activation of inflammatory factors, such as insulin resistance, inflammatory cytokines, and leukocyte dysfunction [4].

There are two types of DM; one is caused by a genetic factor and the other is due to a metabolic disorder such as obesity that is related to a less active lifestyle [27]. Generally, streptozotocin (STZ) is the most commonly used agent in the experimental induction of type 1 DM with an underlying genetic factor [24,25]. STZ-induced DM displays the characteristics of hyperglycaemia, insulin deficiency, and chronic pro-inflammatory state [4,9].

Regular aerobic exercise and standard pharmacologic treatment are used for the prevention and treatment of diabetes [9,12]. In particular, regular physical exercise has marked anti-inflammatory effects in DM [4] and so may be an effective approach to protect diabetics against microbe-related infection, insulin resistance, and vascular complications [13]. Previous studies on exercise training focused on reduction of the risk factors associated with inflammation, and on the role of aerobic exercise and resistance training in the regulation of inflammation and the immune response [3,16]. The results concerning the anti-inflammatory effects of exercise have been varied, reflecting differences in the type of exercise, duration of exercise, exercise intensity, endurance capacity, and muscle morphology [3,7,30].

The anti-inflammatory mechanisms of regular exercise training need further detailed study to clarify the role of exercise intensity on alleviation of chronic inflammatory diseases, especially DM. The present study was undertaken to address the hypothesis that high- and low-intensity exercise training will produce different anti-inflammatory effects in DM.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats (243 ± 7 g, 8 weeks) were kept in a room with an alternating 12-h light/dark cycle under standardized conditions of temperature and humidity. Forty animals were divided into eight groups (n=5 per group): non-exercise control (NEC); non-exercise diabetic (NED); acute bout of high-intensity exercise control (AHC); acute bout of high-intensity exercise diabetic (AHD); training high-intensity exercise control (THC); training high-intensity exercise diabetic (THD); training low-intensity exercise control (TLC); and training low-intensity exercise diabetic (TLD). Exercise consisted of a physical training programme on a treadmill. Standard animal laboratory chow consisting of 56.8% carbohydrate, 22.5% protein, 3.5% lipids, and 17.2% other nutrients (Korea Animals) and water was given ad libitum. The experiment was approved by the Ethical Committee of the Chonbuk National University (CNU: 2012-0036) and followed the guidelines for care and use of laboratory animals.

Induction of diabetes

Experimental diabetes was induced by peritoneal injection of 50 $mg \cdot kg^{-1}$ STZ dissolved in sodium citrate buffer (pH 4.5). Forty-eight hours after STZ injection, the diabetic state was confirmed by elevation of blood glucose to >300 $mg \cdot dl^{-1}$ as estimated with an Accu-Chek Active glucose meter (Roche Diagnostics GmbH, Mannheim, Germany) [26]. Blood samples were obtained from a cut at the tip of the animal's tail.

Physical training protocol

The exercise protocol has been described previously [23]. Briefly, in the first week of the preliminary experiments, the rats were adapted to an Omnipacer model LC-4 treadmill (Omnitech Electronics, Columbus, OH, USA). The adaptation consisted of 10–15 min of exercise at a speed of 5–10 $m \cdot min^{-1}$ on a 0° incline. During the first 1 week of training, the running speed was set at 7–15 $m \cdot min^{-1}$ at an incline of 0–5° incline for 60 min (low- and high-intensity training exercise). For the next 2 weeks, the running speed was set at 10–22 $m \cdot min^{-1}$ on a 0–10° incline for 50–60 min. For the remaining 4 weeks, the running speed and duration of training were gradually increased to 27 $m \cdot min^{-1}$ on a 10° incline for 60 min (high-intensity) and 12 $m \cdot min^{-1}$ on a 0° incline for 60 min (low-intensity), 5 days a week for 6 weeks, with increased effort per session starting from 10 min at 10 $m \cdot min^{-1}$ up to 20 min at 27 $m \cdot min^{-1}$. Every 10 min the treadmill was slowed to 10 $m \cdot min^{-1}$ for 1 min. Electric shocks were used sparingly to motivate the animals to run. Electrical shocks were applied to the metal grid behind the lane to stimulate rats that failed to run spontaneously. The non-exercise group remained in their cages. Rats were sacrificed immediately after the last acute bout of exercise after the 6-week exercise regimen. The samples collected included blood and fast twitch skeletal muscle (extensor digitorum longus, EDL) and slow twitch skeletal muscle (soleus, SOL). The collected plasma and skeletal muscles were stored at –80°C before determination of levels of cytokines and protein activities as described below.

Western blot analysis

Total proteins were extracted from SOL and EDL muscle tissues using a lysis buffer containing 150 mM NaCl, 5 mM EDTA, 50 mM Tri-HCl (pH 8.0), 1%-NP 40, 1 mM aprotinin, 0.1 mM leupeptin, and 1 mM pepstatin, and were quantified using the Bradford dye-binding procedure (Bio-Rad, Hercules, CA, USA). Twenty micrograms of total protein was subjected to 8% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under denaturizing conditions. The resolved proteins were transferred to a Hybond-P membrane (Amersham, Arlington, IL, USA) using a Mini-protein II system (Bio-Rad). After blocking with 5% skimmed milk in phosphate buffered saline (PBS), the membranes were incubated with the antibody to cyclooxygenase-2 (COX-2; Cell Signaling Technology, Beverly, MA, USA), inducible nitric oxide synthase (iNOS; Enzo Life Sciences, Farmingdale, NY, USA), matrix metalloproteinase-2 (MMP-2; Bioworld Technology, Minneapolis, MA, USA), MyoD (Santa Cruz Biotechnology, Santa Cruz, CA, USA), GLUT-4 (Bioworld Technology), and Tubilin (Sigma-Aldrich, St. Louis, MO, USA). Each antibody was diluted 1 : 1000 in 1% skim milk or 3% bovine serum albumin (BSA) for 4 h or 24 h at either 4°C or room temperature. After washing with PBS containing 0.1% Tween-20, once for 15 min and twice for 5 min, each membrane was incubated with anti-mouse or anti-rabbit IgG conjugated to horseradish peroxidase at a 1 : 3000 dilution in PBS for 1 h at room temperature. After the final wash, the immunoreactive bands were detected on Kodak film by enhanced chemiluminescence.

Cytokine measurement

Cytokine concentrations in the supernatants were determined by enzyme-linked immunosorbent assay (ELISA) using OptEIA kits (BD Biosciences, Piscataway, NJ, USA). The plasma levels of interleukin IL-6, IL-4, IL-1β, and tumour necrosis factor-alpha (TNF-α) were analyzed according to the manufacturer's instructions. One hundred microlitres of each serum was mixed with assay buffer according to the manufacturer's instructions. The absorbance was measured at 420 nm using a Synergy 2 ELISA plate reader (Bio-Tek, Winooski, VT, USA).

Total nitric oxide (NO) analysis

NO concentration in serum was measured using a total nitric oxide assay kit (Stressgen, Ann Arbor, MI, USA) based on the modified Griess reaction [10]. The calculated concentration was taken as an indicator of NO production. One hundred microlitres of each supernatant was mixed with assay buffer according to the manufacturer's instructions and absorbance (optical density) was determined using the aforementioned ELISA plate reader at 550 nm.

Superoxide dismutase (SOD) and malondialdehyde (MDA) measurements

The SOD assay measures all three types of SOD (Cu/Zn, Mn, and FeSOD). The plasma level of SOD was measured using a SOD assay kit (Cayman Chemical, Ann Arbor, MI, USA). The optical density at

440-460 nm was measured using a microplate reader. The measurement of thiobarbituric acid reactive substances (TBARS) is a well-established method for screening and monitoring lipid peroxidation. The plasma level of MDA was measured using a TBARS assay kit (Cayman Chemical, Ann Arbor, MI, USA). The optical density at 530-540 nm was measured using a microplate reader.

Statistical analyses

Group comparisons were assessed by one-way analysis of variance (ANOVA) and Student-Newman-Keuls post hoc test. Statistical significance was accepted at $p < 0.05$. The values are presented as mean ± SD.

RESULTS

Changes of serum inflammatory cytokines and free radicals according to different intensity exercise training in diabetic rats. DM was induced in experimental rats by injection of STZ. DM was evident by elevation of serum glucose to over 300 $mg \cdot dL^{-1}$ and weight loss (Figure 1A). Since regular physical exercise has known anti-inflammatory effects in DM, we investigated the effect of high- and low-intensity exercise training on blood and skeletal muscles for inflammatory factors. Serum glucose level and weight of the diabetic rats were changed by exercise training. The elevated glucose was lowered by the high- and low-intensity exercise training (THD and TLD), but was unaffected by an acute bout of high-intensity exercise (AHD) ($p < 0.05$) (Figure 1A).

NO and MDA levels increased markedly in diabetic rats. The induced elevation of NO was reduced in the THD and TLD groups, but not in the AHD group (Figure 1B). The MDA level was reduced in all exercise groups (Figure 1C). SOD anti-oxidant activity was enhanced in all exercise groups (Figure 1D). In particular, the THD and TLD groups displayed significant increases in diabetic rats ($p < 0.05$).

IL-1β levels were increased in the diabetic rats. IL-1β was reduced only in the THD and TLD groups ($p < 0.05$) (Figure 2A). The TNF-α level showed the same pattern as the IL-1β level, and its level was reduced in all exercise groups (Figure 2B). In particular, the level in the TLD group was markedly decreased compared to the NED group of diabetic rats ($p < 0.05$) (Figure 2B). IL-6 levels were increased in the diabetic rats, and the levels were reduced effectively in all exercise groups (Figure 2C). In contrast, IL-4 level was increased by the induction of diabetes, especially in the THD and TLD groups ($p < 0.05$) (Figure 2D).

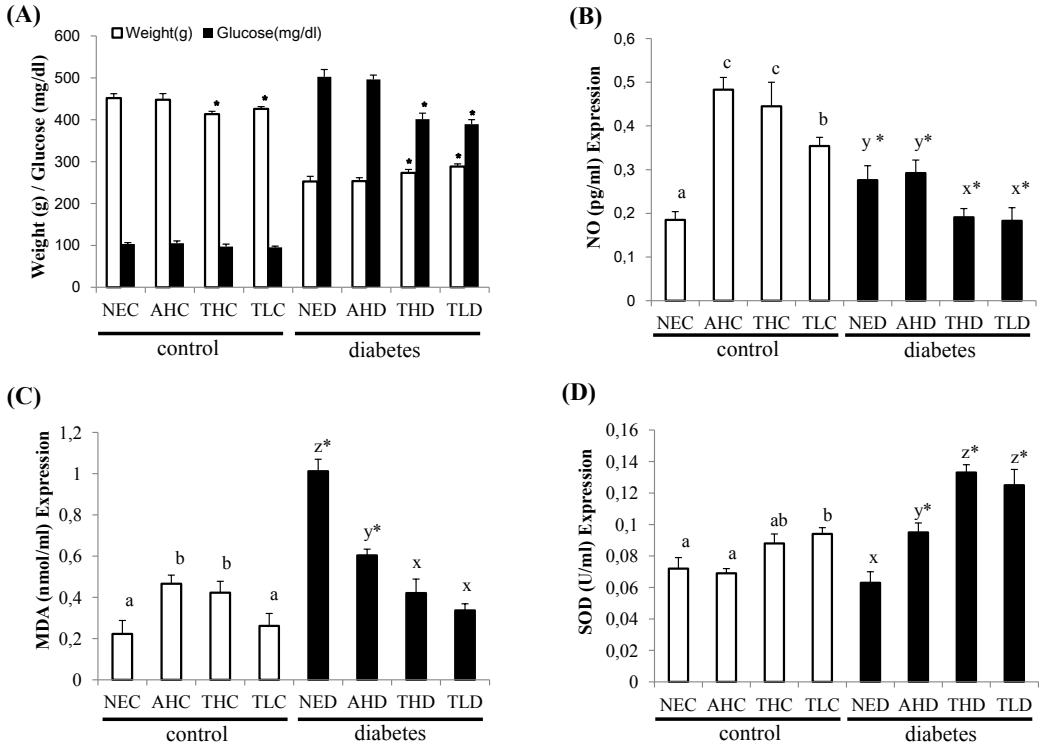

FIG. 1A–D. WEIGHT AND SERUM CONCENTRATIONS OF TARGET COMPOUNDS IN CONTROL AND DIABETIC RATS

Note: Serum levels of glucose (A), NO (B), MDA (C), and SOD (D) were determined and are presented as mean ± standard deviation of five rats per group: non-exercise control (NEC); acute high-intensity exercise control (AHC); training high-intensity exercise control (THC); training low-intensity exercise control (TLC); non-exercise diabetic groups (NED); acute high-intensity exercise diabetic group (AHD); training high-intensity exercise diabetic group (THD); and training low-intensity exercise diabetic group (TLD). The symbols abcd and xyz indicate statistically significant differences compared to each control and diabetic exercise group ($p < 0.05$), respectively. The symbol * indicates statistically significant differences compared to same intensity exercise groups and control ($p < 0.05$).

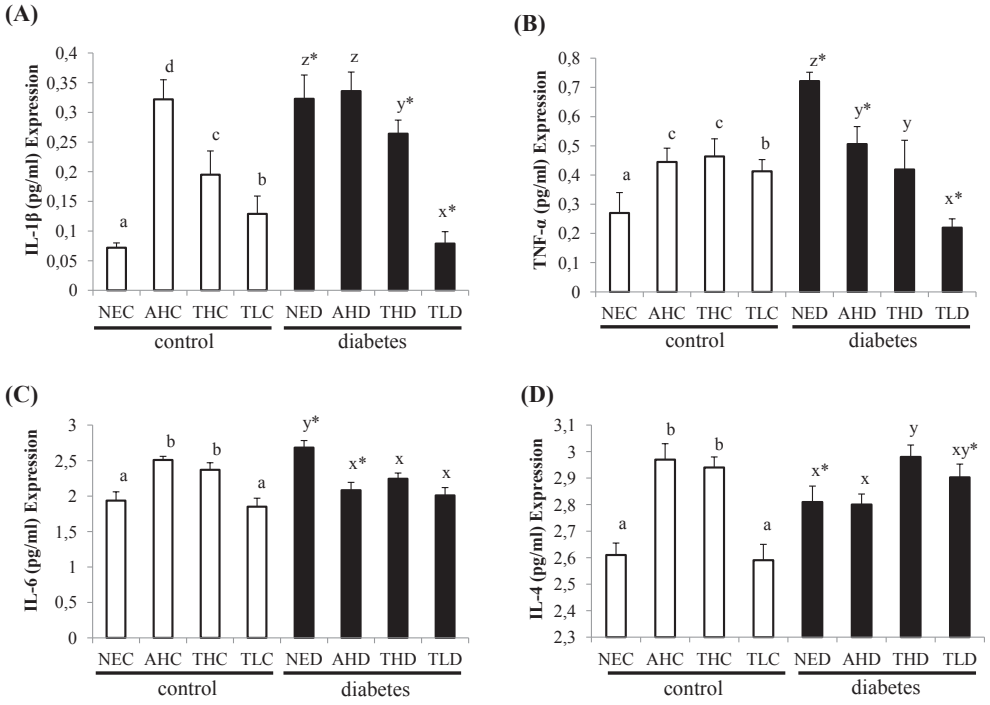

FIG. 2A–D. SERUM CONCENTRATIONS OF IL-1β (A), TNF-α (B), IL-6 (C), AND IL-4 (D) DETERMINED BY ELISA ANALYSIS IN DIABETIC RATS
Note: The values are presented as mean standard deviation of five animals per group ($p < 0.05$). The symbols abcd and xyz indicate statistically significant differences compared to each control and diabetic exercise group ($p < 0.05$), respectively. The symbol * indicates statistically significant differences compared to same intensity exercise groups and control ($p < 0.05$).

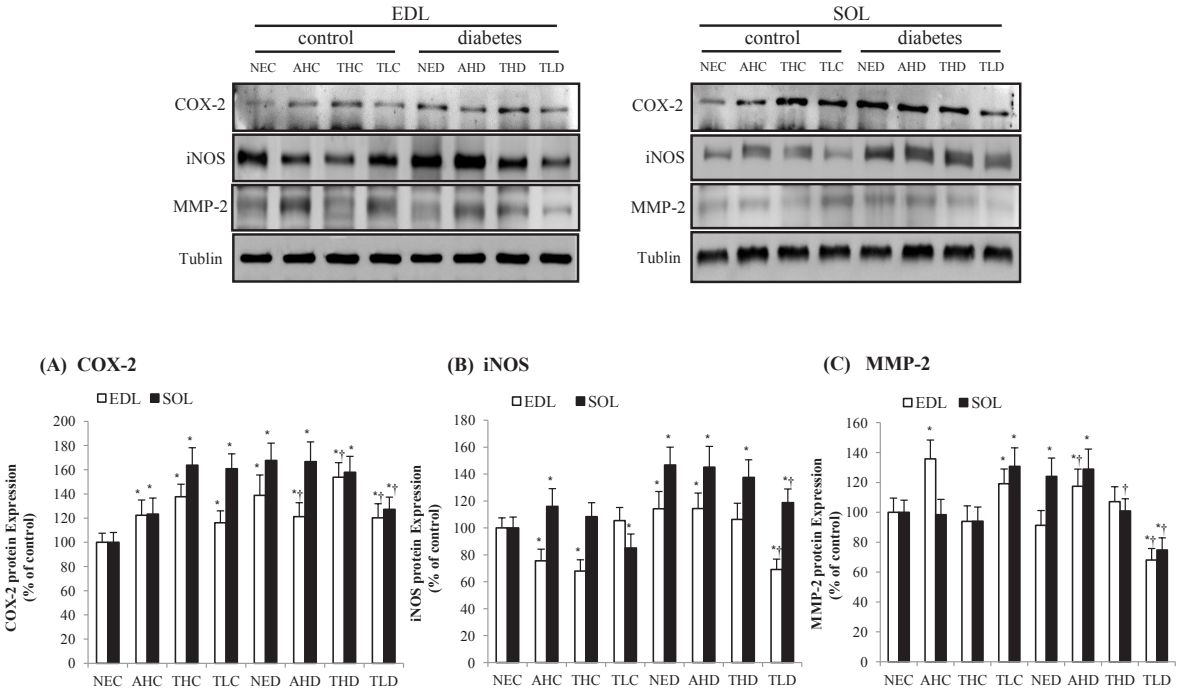

FIG. 3A–C. EXPRESSION OF COX-2, INOS, AND MMP-2 WAS DETERMINED BY WESTERN BLOT ANALYSIS USING SPECIFIC ANTIBODY IN THE EDL AND SOL MUSCLES IN CONTROL AND DIABETIC RATS

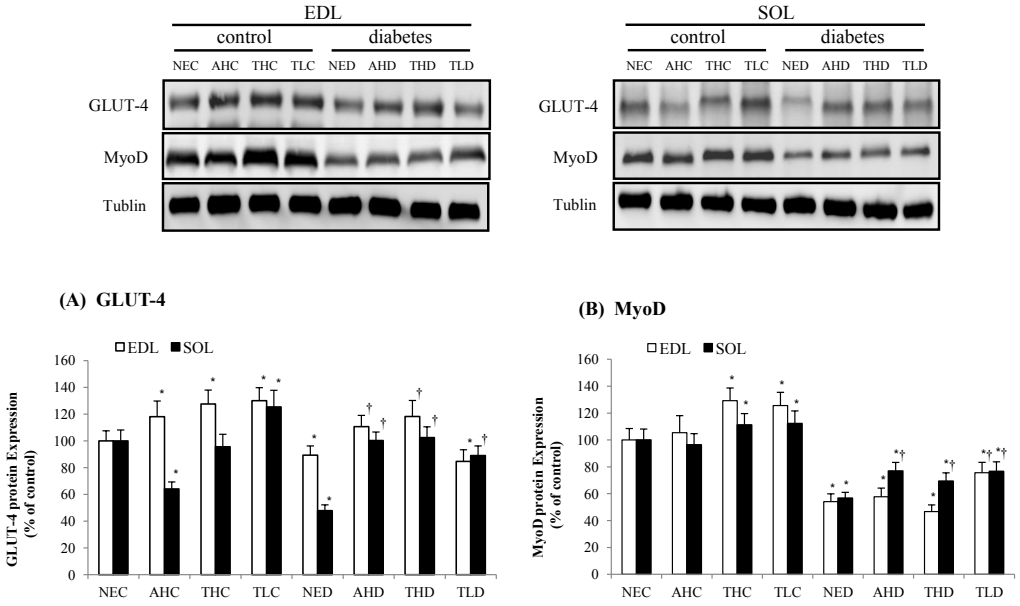

FIG. 4A–B. EXPRESSION OF GLUT-4 AND MyoD DETERMINED BY WESTERN BLOT ANALYSIS USING SPECIFIC ANTIBODY IN THE EDL AND SOL MUSCLES IN CONTROL AND DIABETIC RATS

Changes of inflammatory molecules and glucose uptake activity according to the intensity of exercise training in skeletal muscles of diabetic rats

The effect of exercise training on inflammatory molecules and glucose uptake was evaluated in EDL and SOL skeletal muscles of diabetic rats. The levels of the COX-2, MMP-2, and iNOS inflammatory molecules were increased in diabetic rats, but intensity exercise training reduced the levels of these molecules in both EDL and SOL muscles (Figures 3A and B and C). The most effective exercise training was low-intensity exercise training (TLD) in the diabetic rats.

The levels of the GLUT-4 glucose uptake factor were analyzed in the skeletal muscles. GLUT-4 expression was reduced in diabetic rats, but the reduced expression was recovered by all exercise training (Figure 4A). The most effective training type to elevate GLUT-4 was THD. Muscle growth factor MyoD also showed the same expression pattern (Figure 4B).

DISCUSSION

Hyperglycaemia in diabetes results in the production of free radicals, induction of inflammation, and reduction of various defence mechanisms [29]. Exercise therapy, rather than drug treatment, has been recommended to combat insulin resistance and hyperglycaemia [4]. In this study, we investigated the anti-inflammatory effect of acute exercise, and high- and low-intensity endurance exercise in slow-twitch skeletal muscle fibre (SOL) and fast-twitch skeletal muscle fibre (EDL) muscle in rats following induction of diabetes using STZ.

NO-mediated damage of skeletal muscle occurs following its activation because of exercise influenced inflammatory reaction and anti-oxidant enzymes in skeletal muscles [4,5,17]. Presently, NO levels were increased in the AHC group and in diabetic rats; the NO elevations were reduced by high- and low-intensity exercise training. In addition, an elevated level of NO resulted from acute high-intensity exercise, but NO did not damage skeletal muscles in normal conditions. However, a continuous high level of NO in DM causes inflammation, which in turn results in damage to skeletal muscles. The present observation of the down-regulation of NO in the THD and TLD groups suggests that regular exercise training is advantageous to reduce the DM-induced inflammatory reaction.

MDA displayed a similar pattern as NO. Long-term exercise training in diabetes reportedly increases SOD activity and decreases the level of MDA [14]. These prior observations are consistent with our finding that regular exercise training affects the anti-oxidant activity in diabetic rats. In particular, the most effective exercise training reduced ROS and activated SOD in low-intensity exercise training in diabetic rats. The present and previous findings reinforce the view that regular exercise training is important in management of DM. Additionally, while the inflammatory cytokines IL-1β, IL-6, IL-4, and TNF-α were increased in diabetic rats, exercise effectively reduced these elevated levels. In particular, the induced increases in IL-1β and TNF-α were markedly decreased in the TLD and THD groups compared with the AHD group. Low- and high-intensity exercise training quelled the elevations in the inflammatory molecules and cytokines, even though exercise induced an inflammatory reaction.

Therefore, regular exercise rather than the intensity of exercise is physiologically important in reducing diabetes-induced inflammation.

The specific response induced by diabetes activates inflammatory molecules that include COX-2 and iNOS [8]. COX-2 is also involved in inflammatory and immune responses activated by inflammatory cytokines [8]. In addition, activation of iNOS strongly promotes the production of NO in the hyperglycaemic state. In these pathological conditions, the iNOS pathway is activated by inflammatory cytokines and molecules [22]. In this study, COX-2 and iNOS were significantly induced in diabetic rats, but regular exercise training reduced DM-induced inflammatory molecules in both slow twitch and fast twitch skeletal muscles (SOL and EDL, respectively). It is well known that exercise training activates ROS and inflammation, but also bestows anti-oxidant activity. In particular, regular low-intensity exercise training inhibits various inflammatory inducible factors including COX-2 and iNOS in DM-induced skeletal muscle.

Matrix metalloproteinases (MMPs) are related to inflammation, cell invasion, metabolism, apoptosis, and muscle growth and development [6]. High-intensity exercise markedly increases MMP-2 levels in glycolytic fibres of healthy skeletal muscles [7]. This suggests that muscle damage by intense exercise involves the expression of MMPs. However, in this study, MMP-2 was significantly reduced in the TLD group of diabetic rats. Thus, in the diabetic state, low-intensity exercise, but not high-intensity exercise, was more effective in reducing MMP-2 levels.

GLUT-4 participates in glucose transport and movement in carbohydrate metabolism, and is the key regulator to reduce insulin resistance in DM [18]. In particular, GLUT-4 is induced through the insulin-independent pathway by exercise, and improves insulin sensitivity by promoting glucose transport [11]. In this study, the GLUT-4 level was increased significantly by all types of exercise even in diabetic rats. Particularly, GLUT-4 levels were increased more in the high-intensity exercise groups of diabetic rats than in the low-intensity exercise groups, consistent with previous results [15]. In addition, GLUT-4 in diabetic patients is also increased after acute and long-term endurance training [19]. Therefore, regular exercise training is recommended for improved glucose uptake for diabetics, since GLUT-4 is increased regardless of the intensity of exercise.

MyoD also contributes to muscle fibre regeneration [20]. In addition, the level of MyoD changes according to skeletal muscle characteristics, exercise method, and exercise intensity [21]. In this study, MyoD was increased by low-intensity exercise in diabetic rats, suggesting that among the various exercise options low-intensity exercise training is relatively effective in combating muscle atrophy caused by diabetes. In addition, high-intensity exercise is more prone to exercise overuse, and subsequent muscle tissue damage and functional decline, than low-intensity exercise.

CONCLUSIONS

In summary, regular exercise training inhibits inflammatory molecules and cytokines in blood and skeletal muscles against DM-induced stress. Low-intensity exercise training is most effective in reducing DM-associated pathology. Different exercise types, such as acute, high-intensity, and low-intensity exercise, are an essential part of the therapeutic stratagem for recovery of skeletal muscle derived from a complex disease like diabetes. The effect of low-intensity exercise may be ascribed to the anti-inflammation response by removal of ROS formation, rather than acute exercise. Also, optimal exercise training according to the type of disease is crucial for the treatment of chronic complicated diseases that are accompanied by an inflammatory response.

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