Preventive effect of weight-bearing in disuse muscle atrophy of diabetic rats

Original Article

Journal of Wellness and Health Care Vol. 45 (1)
33～40 2021

Preventive effect of weight-bearing in disuse muscle atrophy of diabetic rats

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Abstract

Purpose: Diabetes is associated with various health complications including disuse muscle atrophy. We aimed to examine the preventative effect of weight-bearing for disuse muscle atrophy in Wistar and Goto-Kakizaki rats undergoing the tail suspension method.

Subjects and Methods: We divided Wistar and Goto-Kakizaki rats into three groups (n=8 for both): a control group, suspension group and weight-bearing group. The target muscles were the soleus and plantaris. We then performed hematoxylin-eosin staining and observed the muscle samples using an optical microscope.

Results: For the soleus muscle, Wistar rats and Goto-Kakizaki rats showed the same tendencies, and a certain degree of atrophy-prevention due to weight-bearing was observed in the muscle fiber cross-sectional area. As for the plantaris muscles, Wistar rats and Goto-Kakizaki rats showed the same tendencies, however the atrophy-preventing effect in the Goto-Kakizaki rats was minor.

Conclusion: The type of myofiber predominance in the soleus and plantaris muscles may be associated with the degree of recovery in the myofiber cross-sectional area resulting from weight-bearing in rats undergoing the tail suspension method.

KEY WORDS

tail suspension, weight-bearing, diabetic rat

Introduction

The number of people with diabetes is steadily increasing worldwide and, in Japan, the 2017 National Health and Nutrition Survey found that the proportion of people who were strongly suspected of diabetes was 18.1% for males and 10.5% for females, for a total of more than 10 million people[1]. Diabetic patients are more likely to develop atherosclerosis, and the risk of cerebral or myocardial infarction is reported to be 2-4 times that of non-diabetic patients[2,3]. In addition, when diabetic neuropathy is involved, it is considered that the risk of falling is significantly increased due to impaired foot sensation and decreased range of motion of the joints. Therefore, a diabetic patient with complications such as a cerebral infarction, myocardial infarction, or a fracture due to a fall, is forced to rest and is highly likely suffer from disuse muscle atrophy.

Animal experiments for disuse muscle atrophy are frequently performed, and it has been reported that reloading of muscle atrophy due to hind-limb suspension and cast fixation can assist recovery from atrophy[4]. On the other hand, skeletal muscle that has once atrophied is fragile, and a possibility of muscle damage has been reported, depending on the load[5,6]. In a report by Zushi[7] on load stimulation for disuse muscle atrophy in rat soleus muscles, muscle regeneration was shown to be accompanied by muscle damage, while at the same time there was generation of small diameter fibers and an increase in central nucleus fibers. These experimental results are true for standard Wistar rats and show the effect of intervention on muscles that have once atrophied.

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In recent years, it has been reported that diabetic patients have reduced muscle mass compared to healthy people of the same age[8,9]. In a previous study, we used a tail-suspension method to induce disuse muscular atrophy in Goto-Kakizaki (GK) rats—which are non-obese type 2 diabetes model rats—and then reloaded them. The soleus muscle showed similar results to Wistar rats, but the plantaris muscle was reported to only show a decrease in muscle fiber cross-sectional area and insufficient recovery in GK rats only[10]. It has been reported that recovery of the cross-sectional area of the soleus muscle after disuse muscle atrophy requires more than 2 weeks[7], and prevention of atrophy by early intervention is an important issue in rehabilitation.

In the clinic, the prevention of disuse by early intervention rehabilitation is being actively carried out, and getting out of bed interventions are being carried out as early as possible. In animal studies, it was reported that during the hind-limb suspension period of the rat, loading was not completely effective in preventing disuse muscle atrophy, but it was able to alleviate the decline in muscle output and muscle capacity[11]. However, it is unclear whether a preventive effect is similarly obtained for the muscles of diabetic patients, who are said to have reduced protein synthesis. Therefore, in this study, we decided to induce disuse muscular atrophy in GK rats by using the tail-suspension method, apply a load in the process, and examine the preventive effect on disuse muscular atrophy. We believe that this study will help establish a method of exercise for the prevention of disuse muscle atrophy in diabetic patients. The target muscles were the soleus muscle and the plantaris muscle. In the soleus muscle, many of the muscle fibers are composed of type I fibers and have been used in many previous studies. Plantaris is a muscle in which type I, type IIA, and type IIB fibers are mixed as a type distribution, and although there is little change compared with the soleus muscle, atrophy and rapid muscle formation characteristic of non-loading are observed[12].

Methods

Forty-eight rats (24 Wistar and 24 GK rats) initially aged 8 weeks were used in this study. The experimental protocol was previously approved by the Kanazawa University Ethics Committee for Animal Experiment (no. AP-153551).

The Wistar (W) and GK rats (G) were randomly divided into six groups (n=8 per group): Wistar Control (WC), GK Control (GC), Wistar Suspension (WS), GK Suspension (GS), Wistar Weight-bearing (WW) and GK Weight-bearing (GW). The Control groups were kept under normal conditions (WC and GC). The Suspension groups underwent tail suspension for one week (WS and GS). The Weight-bearing group underwent weight-bearing for one hour/day during the one-week tail-suspension period (WW and GW). Zushi[13] reported a decrease in muscle cross-sectional area after 1-week of hind limb suspension, and thus the suspension period in this study was set to 1 week in this study. The tail suspension was performed over a week and the method was according to that described by Morey-Holton et al.[14]. Non-elastic tape was wrapped around the lateral sides of the central caudal region of the rats under isoflurane gas anesthesia. The rats were then suspended from the roof of the cage allowing their front legs to be in contact with the cage floor for free locomotion in the cage. The animals had free access to food and water (HydroGel). The room temperature was maintained at approximately 22℃ and with a 12 h light-dark cycle environment to prevent interference with the rat's biological rhythm.

At the end of the experimental period, under isoflurane anesthesia, the rat's body weight was measured; blood samples were taken, and their blood glucose levels were measured. The blood glucose level was set to the fasting blood glucose, and the animal was fasted for at least 10 hours at the blood sampling point. Their soleus and plantaris muscle were surgically resected and the muscles wet weights were measured. The resected muscles were frozen in isopentane solution, cooled in liquid nitrogen and stored at a temperature of -80℃ until further analysis. Later, cross-sectional cryosections of 10 μm were prepared from the middle of the muscle samples (along the length of the muscle) using a cryostat. After naturally drying out the frozen sections at room temperature, the samples were observed using an optical microscope after hematoxylin-eosin staining[10]. To determine the level of muscle atrophy, we randomly selected a minimum of 150 myofibers per stained slice image. Ceglia[15] reported

that the measurement of the cross-sectional area of more than 150 muscle fibers provides good reliability. The ImageJ free software (Ver.1.46r) was used for image analysis and to measure the cross-sectional areas. To analyze the muscle damage, we calculated the onset rate of centrally nucleated fibers and myofiber necrosis compared to whole fiber numbers. Myofiber necrosis was identified by the presence of phagocyte infiltration or markedly lighter staining[16].

One-way ANOVA was used to assess the body weight; blood glucose levels; wet weights of both the soleus and plantaris muscles; muscle weight/body weight ratios; and myofiber cross-sectional areas of samples in the Control, Suspension, and Weight-bearing groups. Tukey tests were performed to assess sub-effects. The onset rates for myofiber necrosis and centrally nucleated fibers were subjected to the chi-squared test and Bonferroni correction. All statistical analyses were performed using the software SPSS, version 23 (IBM SPSS). Significance level was set at 5%.

Results

Blood glucose levels at the time of the animals' sacrifice were 173.4±35.3 mg/dl for the Wistar rats and 305.0±45.7 mg/dl for the GK rats. The GK rats had significantly higher blood glucose levels in comparison to the Wistar rats.

Table 1 shows the mean ± standard deviation (SD) values for the body weight, the muscle wet weight, the muscle weight/body weight (at the time of the sacrifice) ratio, and the myofiber cross-sectional areas for the soleus (Table 1a) and plantaris muscles (Table 1b).

The WW and WS groups had significantly lower body weight values than the WC group . The WS group body weight was significantly lower than the WW values. In GK rats, GS and GW groups had significantly lower body weight values than the GC group. The muscle weight/body weight ratio of the soleus muscle in Wistar rats was significantly lower in WS and WW groups than in the WC group. In GK rats, the GS group was significantly lower than the GC group, and the GW group was significantly larger than the GS group. There was no significant difference between GC group and GW group. In the plantaris muscles, Wistar rats had significantly lower muscle weight/body weight ratio in WS group than WC group. For GK rats, as in the soleus muscles, the GS group decreased compared to the GC group, and was larger in the GW group than the GS group.

Regarding the muscle fiber cross-sectional area, the soleus muscle of the Wistar rats was significantly smaller in the WS and WW groups than in the WC group, and significantly larger in the WW group than in

Table 1. Group characteristics of soleus and plantaris muscles

a. Group characteristics of soleus muscle

	Wistar			GK		
Groups	WC	WS	WW	GC	GS	GW
Pre-BW(g)	194.±9.2	202.9±9.4	201.4±5.3	203.4.±9.2	204.6±5.7	213.6.±10.0
Post-BW(g)	215.3±12.2	178.6±8.8*	192.6±10.5* †	212.9±13.1	188.5±7.8*	190.4±8.3*
MW (mg)	90.6±5.9	52.1±7.3*	61.5±4.5* †	85.6±6.9	52.6±5.2*	66.6±3.8* †
MW/BW (mg/g)	0.42±0.02	0.29±0.04*	0.32±0.01*	0.40±0.04	0.28±0.043*	0.36±0.03 †
MCSA (μm^2)	2172±189	1231±172*	1599±207* †	2313±166	1671±339*	1907±149* †

b. Group characteristics of plantaris muscle

	Wistar			GK		
Groups	WC	WS	WW	GC	GS	GW
Pre-BW(g)	194.±9.2	202.9±9.4	201.4±5.3	203.4.±9.2	204.6±5.7	213.6.±10.0
Post-BW(g)	215.3±12.2	178.6±8.8*	192.6±10.5* †	212.9±13.1	188.5±7.8*	190.4±8.3*
MW (mg)	216.0±9.9	151.0±28.0*	173.5±7.3* †	203.2±11.9	148.6±8.8*	169.5±9.1* †
MW/BW (mg/g)	1.00±0.04	0.85±0.17*	0.90±0.03	0.96±0.08	0.79±0.04*	0.90±0.06 †
MCSA (μm^2)	2331±377	1707±277*	1813±297*	2051±190	1535±265*	1579±209*

Pre-BW, Pre-experiment weight, Post-BW, Post-experiment weight, MW, wet weight; MW/BW, muscle weight/Post-body weight ratio; CSA, myofiber cross sectional area

Values are shown as mean±SD
* : Significant differences between Wistar and GK rats and the Control group ($p<0.05$)
† : Significant difference compared to the Suspension group ($p<0.05$)

the WS group. In GK rats, the GS group and the GW group were significantly smaller than the GC group. The plantaris muscle showed similar results to Wistar rats and GK rats, and the Suspension group and the Weight-bearing group were significantly smaller than the Control group. In addition, graphs showing the ratios of the muscle fiber cross-sectional area for each size are shown in Fig. 1 and Fig. 2. Both the soleus and plantaris muscles showed the same tendency in Wistar rats and GK rats.

Table 2 shows the proportion of necrotic fibers and central nucleus fibers to all the measured fibers. Neither the number of necrotic fibers nor the number of centrally nucleated fibers showed any significant difference between the groups.

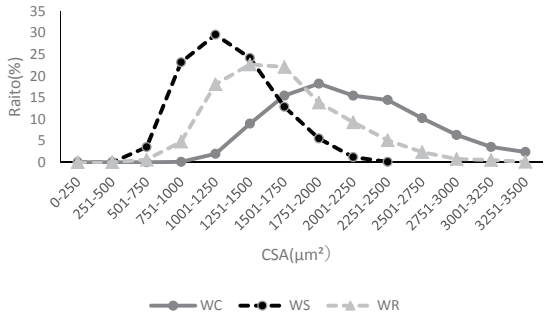

Fig.1a

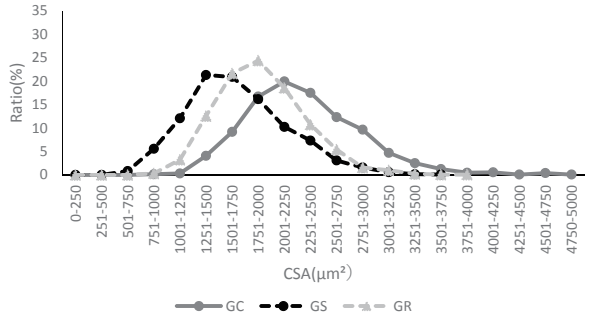

Fig.1b

Figure 1 a, b: Soleus myofiber cross-sectional area distributions
1 a: Myofiber cross-sectional area distribution for Wistar rats in all groups
1 b: Myofiber cross-sectional area distribution for GK rats in all groups
The peak in the Suspension group for both types of rats shifted to the left, indicating muscle atrophy.
Compared to the Suspension group, the peak in the Reload group shifted right, indicating a tendency toward recovery of myofiber cross-sectional area.

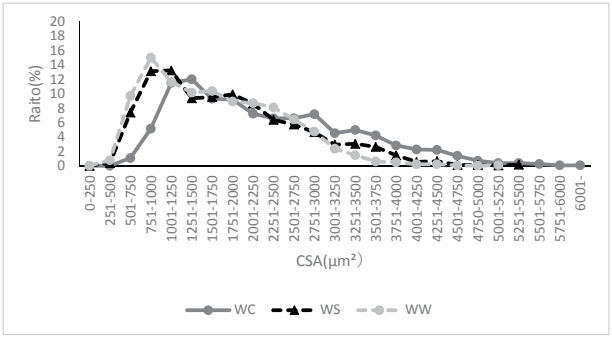

Fig.2a

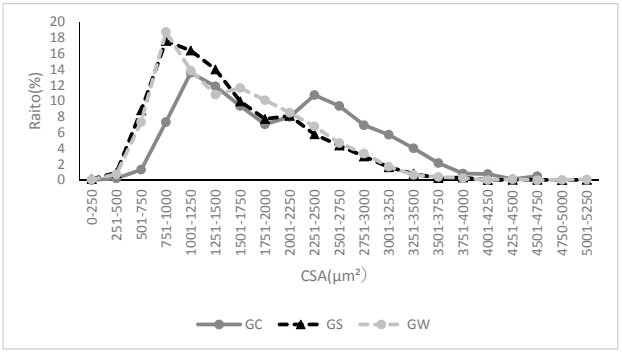

Fig.2b

Figure 2 a,b: Plantaris muscle myofiber cross-sectional area distribution
2 a: Myofiber cross-sectional area distribution for Wistar rats in all group
2 b: Myofiber cross-sectional area distribution for GK rats in all groups
Although there were no major differences between the Wistar rats among groups, a higher number of rats in the WS and WR groups tends to have smaller cross-sectional areas.
A similar tendency was observed in GK rats.

Table 2. Rates of myofiber necrosis and centrally nucleated myofibers (%)

Muscle	Soleus		Plantaris	
Group	Necrosis	CN fiber	Necrosis	CN fiber
WC	0.18	1.05	0.13	0.19
WS	0.26	0.5	0.05	0
WW	0.33	0.8	0.26	0.04
GC	0.42	1.5	0.28	0
GS	0.28	0.8	0.41	0
GW	1.61	1.4	0.15	0.15

CN, Centrally nucleated fiber
No significant differences were observed between soleus and plantaris muscles in the C, S, or W groups for either the Wistar or GK rats.

Discussion

In this study, GK rats (non-obese type 2 diabetic rat model animals), were used to compare the preventive effects of weight-bearing on disuse muscle atrophy with Wistar rats. In this study, both Wistar rats and GK rats lost weight in the experimental group compared to the control group. This is a result similar to many previous studies[4-7,13],, and the hindlimb suspension model causes

not only disuse muscular atrophy, but also negative effects in terms of bone metabolism, water metabolism, and body fluid electrolyte composition, being adopted as an experimental model created to simulate to the state of long-term bed rest in humans[14]. Therefore, similar to long-term bed rest in humans, it is probable that weight loss was observed in this study. Onda[17] also reported that although there was no significant difference in food intake between the control group and the hindlimb suspension group, there was a significant difference in body weight, and weight loss in the hindlimb suspension model suggesting the involvement of factors other than food intake. In this study, food intake was not measured however it is preferable to be measured in future studies and examine its effect on body weight.

The relative muscle weight/body weight ratio of both the soleus and plantaris muscles was significantly lower in the Suspension group than in the Control group for both Wistar rats and GK rats. This may be the result of muscle atrophy with tail suspension, as in various previous studies. On the other hand, there was a significant difference between the soleus muscles of the WC and WW groups, but no significant difference between the GC group and the GW group. There was no significant difference in the plantaris muscle between the WS group and WW group, and significant difference was observed between GS group and GW group.

Muscle mass depends on the balance between protein synthesis and degradation. Muscle fibers enlarge when the balance leans toward protein synthesis and shrink when leaning toward degradation[18,19]. This is controlled by the intracellular signal transduction system, and the intracellular signal transduction molecules are activated by mechanical stimuli such as weight bearing[20,21]. It is possible that the GK rats received a stronger response to reloading mechanical stimuli than the Wistar rats, leading to suppression of atrophy. However, there is a report that type 2 diabetes may reduce the balance between protein degradation and synthesis in skeletal muscle, due to insulin resistance, and may lead to a decrease in skeletal muscle mass more than usual[22,23].

Wistar rats significantly decreased muscle fiber cross-sectional area of the soleus muscle, in the order of WC group, WW group, and WS group; in the GK rats' group, similarly in the order of GC group, GW group, GS group. Regarding the plantaris muscles, in both Wistar rats and GK rats, the Suspension group and the Weight-bearing group were significantly reduced as compared with the Control group. Although no significant difference was observed, in the Wistar rats, the Weight-bearing group showed a larger value than the Suspension group. On the other hand, in GK rats, there was almost no difference between the Suspension group and the Weight-bearing group.

Regarding the soleus muscle, in previous studies it was possible to suppress the progression of disuse muscle atrophy by weight-bearing[18], and in this study it is considered that the progression of muscle atrophy was suppressed in both the Wistar rats and the GK rats by load. On the other hand, with respect to the plantaris muscles, although the progress of weight-bearing was suppressed to some extent in the Wistar rats, the results were small in the GK rats. In our study with a one-week reload after two-week tail suspension, we found that solely GK rats showed significant atrophy of muscle fiber cross-sectional area and poor recovery in the plantaris muscles. Aged GK rats exhibited a decrease in the ratio of fiber types with high oxidase activity, and the proportion of soleus muscle type IIA fibers decreased leaving primarily type I fibers, while, in the plantaris muscle, the ratios of both type I and type IIA fibers decreased and transitioned to type IIB fibers[24,25]. Regarding the plantaris muscles, the atrophy of fast muscle fibers precedes slow muscle fibers in type 1 diabetic rats[26]. Similar plantaris muscle results are also observed in GK rats, which are type 2 diabetic rats. It is presumed that the atrophy of type IIB fiber precedes most of the time, so that it was more strongly affected by the suspension, and that the effect of preventing muscle atrophy due to the load was difficult to see. It is possible that these differences in the muscle fiber types of Wistar rats and GK rats influence the differences in the preventive effects of muscle cross-sectional area reduction due to the load during tail suspension.

This study observed necrotic fibers and central nucleus fibers as indicators of muscle damage. Necrotic fibers occur when mechanical or scientific damage is applied to skeletal muscle. Normally, active regeneration occurs after the occurrence of necrotic

fibers in the central nucleus[16]. In this study, there was no significant difference in the percentage of central nucleus generation and the percentage of necrotic fiber generation between the Wistar rats and the GK rats in both the soleus and plantaris muscles. On the other hand, Ferreiral[27]. reported the occurrence of central nuclear fibers in the process of muscular atrophy, albeit slightly. However, in this study, there was no significant difference between all groups, so it is not possible to estimate the factors behind the occurrence of central nuclear fibers.

In the soleus muscle of GK rats, there is a report of a decrease in peripheral vascular volume[22] and a weakness in the soleus muscle of type 1 diabetes model rats due to a decrease in the number of motor neuron cells[24]. It has been reported that insulin acts as an anabolic hormone, suppresses muscle protein degradation and promoting muscle protein synthesis[25], and when insulin resistance is increased due to diabetes, protein metabolism may be adversely affected. It is suggested that the muscle fibers of the GK rat soleus, as well as the vascular and nervous tissues, may be weakened by the effects of insulin resistance and hyperglycemia exposure. As a limitation of this study, we conducted research on morphological aspects such as muscle fiber cross-sectional area, but we have not accurately studied the measurement of muscle protein and insulin levels. This will need to be clarified through further investigation. In addition, it is considered that further analysis was required for weight loss, such as measuring the amount of food intake, and so for nutritional status, such as albumin level. In addition, it is necessary to consider each muscle fiber type. Since the subjects undergo short-term interventions for young rats for one week, it is necessary to extend the study and confirm the effects on old rats.

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糖尿病ラットの廃用性筋萎縮に対する荷重の予防効果

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要　旨

本研究では，2 型糖尿病モデルラットである Goto-Kakizaki ラット（以下 GK ラット）に対し，尾部懸垂法を用い廃用性筋萎縮を作成し，その過程において荷重を加え，萎縮予防効果について検討することとした。対象は 8 週齢の Wistar 系ラット 24 匹，GK ラット 24 匹とした。Wistar 系ラット，GK ラットをそれぞれコントロール群 (WC 群：n ＝ 8，GC 群：n ＝ 8) と 1 週間尾部懸垂する懸垂群 (WS 群：n ＝ 8，GS 群：n ＝ 8)，1 週間の尾部懸垂期間中毎日 1 時間荷重する群 (WR 群：n ＝ 8，GR 群：n ＝ 8) に群分けした。ヒラメ筋と足底筋を実験終了後，摘出し相対重量比，筋線維横断面積を中心に分析を行った。ヒラメ筋・足底筋ともに相対重量比では，Wistar 系ラット，GK ラットとも懸垂群はコントロール群に比較し有意に低下していた。筋線維横断面積については，ヒラメ筋では Wistar ラット，GK ラットともに同様の傾向を示し，荷重によるある程度の萎縮予防効果がみられたが，足底筋については，GK ラットの荷重による萎縮予防効果はより小さかった。糖尿病ラットでは，遅筋線維に先行して速筋線維の萎縮が出現すると報告されており，筋線維タイプの違いが尾部懸垂中の荷重による筋横断面積低下の予防効果の違いに影響している可能性が考えられる。今後はさらに筋線維タイプ等の分析も必要と考える。