Growth-Related Changes in Skeletal Muscle Fiber Type and Insulin Resistance in Diabetic Otsuka Long-Evans Tokushima Fatty Rats

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We investigated whether a relationship exists between the fiber type distribution in skeletal muscles and the insulin resistance of different ages of diabetic rats. The fiber type distributions of the slow soleus and fast plantaris muscles in 5-, 9-, and 21-week-old male Otsuka Long-Evans Tokushima Fatty (OLETF) rats as an animal model of spontaneous type 2 diabetes mellitus were examined and compared with those in age-matched non-diabetic Long-Evans Tokushima Otsuka (LETO) rats. In the soleus muscle, a higher percentage of type I fibers was observed in the 9- and 21-week-old OLETF rats compared with the age-matched LETO rats, and there were no type IIA fibers remaining in the soleus muscle of the OLETF rats. In the plantaris muscle, a lower percentage of type IIA fibers and a higher percentage of type IIB fibers were observed in the 9- and 21-week-old OLETF rats compared with the age-matched LETO rats. In addition, a lower percentage of type I fibers in the plantaris muscle was observed in the 9-week-old OLETF rats compared with the age-matched LETO rats, and there were no type I fibers in the plantaris muscle of the 21-week-old OLETF rats. All 20-week-old OLETF rats showed serum insulin concentrations of more than 20 ng/ml. The present study suggests that insulin resistance and impaired glucose tolerance from altered muscle fiber type are linked to the cause of diabetes.

Key words: Enzyme histochemistry, Oxidative capacity, Plantaris muscle, Postnatal growth, Soleus muscle, Type 2 diabetes mellitus

I. Introduction

Non-insulin-dependent (type 2) diabetes mellitus is characterized by impaired insulin secretion and resistance. Insulin-mediated glucose uptake occurs in skeletal muscle, which is the major determinant of insulin sensitivity. Since skeletal muscle is the major target site of insulin-stimulated glucose uptake and disposal, it is considered that patients with type 2 diabetes mellitus have inappropriate metabolic potentials and different patterns of fiber types in skeletal muscle compared with non-diabetic subjects. In fact, patients and animal models of diabetes and/or obesity are known to have a high percentage of low-oxidative type II fibers (particularly type IIB fibers) and a low percentage of high-oxidative type I fibers in the fast skeletal muscles, i.e., the vastus lateralis and rectus abdominis muscles [11, 27, 33]. In addition, these findings in patients concur with a previous study of obesity-prone rats, which showed a high percentage of type II fibers in the fast gastrocnemius muscle compared with non-obese controls [1]. In contrast, there are no studies available regarding the fiber type distributions of slow skeletal muscles, i.e., the soleus muscle, in patients and animal models of diabetes and/or obesity. The normal activity patterns in slow and fast skeletal muscles are different; fibers in slow skeletal muscle are recruited for longer periods at lower activation levels, while fibers in fast skeletal muscle are recruited for relatively brief periods at higher activation levels [36]. In addition, slow skeletal muscles and type I fibers have increased lipid storage capacity [8], increased insulin binding [2, 23],
increased insulin-stimulated glucose uptake [20], and increased glucose transport protein content [9, 29] compared to fast skeletal muscles and type II fibers. Accordingly, slow skeletal muscles in patients and animal models of diabetes and/or obesity could be expected to differ from normal even more than fast skeletal muscles. Therefore, we examined the age-related changes in fiber type distribution and insulin resistance of the slow soleus muscle in insulin-resistant diabetic rats and compared them with the changes in the fast plantaris muscle.

II. Materials and Methods

Experimental animals

Male Otsuka Long-Evans Tokushima Fatty (OLETF) and Long Evans Tokushima Otsuka (LETO) rats at the ages of 5 (n=6 in each group), 9 (n=6 in each group), and 21 weeks (n=7 in each group) were used in the present study. OLETF rats were used as a model of type 2 diabetes mellitus [21]. This diabetic strain with a late onset and chronic course of spontaneous hyperglycemia was established in 1990 by 20 generations of selective breeding and subsequently maintained at the Tokushima Research Institute, Otsuka Pharmaceutical Co. (Tokushima, Japan). The male OLETF rats show rapid body weight gain, visceral obesity (accumulation of intra-abdominal fats), innate polyphagia, impaired glucose metabolism, and insulin resistance in skeletal muscles [16, 20, 37, 38]. The LETO rat never develops diabetes in its entire life and was used as a control.

All rats were individually housed in similar cages. The rats were kept in a controlled environment with a fixed 12 hr light-dark cycle (lights off from 19:00 to 07:00) with room temperature maintained at 22±2°C. Both the OLETF and LETO rats were given food and water ad libitum. All experiments were approved by the Institutional Animal Care and Use Committee at the University and conducted under the Guide for the Care and Use of Laboratory Animals published by the Office of Science and Health Reports of the USA National Institutes of Health.

Tissue preparation

The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg body weight). After blood sampling, the soleus and plantaris muscles on both sides were removed, cleaned of excess fat and connective tissue, and wet-weighed. All rats were sacrificed between 15:00 and 18:00, once a half day was passed after their final meal. The left muscle was placed on cork, stretched to its approximate in vivo length and immediately frozen in isopentane cooled in a mixture of dry ice and acetone. Serial transverse sections, 10 μm thick, from the midbelly region of the muscle were cut in a cryostat microtome set at −20°C.

Fiber type classification

The sections were brought to room temperature, air-dried for 30 min and then stained for adenosine triphosphatase (ATPase) activities following alkaline (pH 10.4) and acid (pH 4.3 and 4.5) preincubation [3, 4]. Classification of fiber types was performed according to the staining intensities following the preincubation of glycine buffers (pH 10.4) or barbital acetate buffers (pH 4.3 and 4.5). For determination of the ATPase activity, the following procedure was employed: alkaline preincubation in 75 mM glycine, 50 mM CaCl₂, and 75 mM NaCl; acid preincubation in 50 mM sodium acetate and 30 mM sodium barbital; and incubation in 2.8 mM ATP, 50 mM CaCl₂, and 75 mM NaCl. After staining for ATPase activity, the sections were processed through 1% CaCl₂, 2% CoCl₂, and 1% (NH₄)₂S, and dehydrated through a graded series of ethanol followed by two changes in xylene, and then coverslipped. The muscle fibers were classified into type I (positive at preincubation pH 4.3 and 4.5, and negative at preincubation pH 10.4), type IIA (negative at preincubation pH 4.3 and 4.5, and positive at preincubation pH 10.4), type IIB (negative at preincubation pH 4.3, and positive at preincubation pH 4.5 and 10.4), and type IIC (positive at preincubation pH 4.3, 4.5, and 10.4). The fiber type distribution of the soleus muscle was determined from the entire transverse section of the muscle, while that of the plantaris muscle was determined from ~500 fibers in the middle region of the transverse section of the muscle. The cross-sectional area of each fiber was measured using a computer-assisted image processing system (Neuroimaging System) on the ATPase-stained (pH 10.4) sections [12, 30, 31].

Succinate dehydrogenase (SDH) activity

The sections were stained for SDH activity, an indicator of mitochondrial oxidative potential, for 10 min at room temperature [5, 6]. The SDH activity was determined in an incubation medium containing 100 mM phosphate buffer (pH 7.5), 0.9 mM sodium azide, 0.9 mM 1-methoxyphenazine methylsulphate, 1.5 mM nitroblue tetrazolium, 5.6 mM EDTA-disodium salt, and 48 mM succinate disodium salt. The reaction was stopped by multiple washings in distilled water. The sections were dehydrated through a graded series of ethanol followed by two changes in xylene, and then coverslipped. Histochemical control sections, in which either the succinate disodium salt or the nitroblue tetrazolium was excluded from the incubation medium, showed no positive SDH staining. The SDH activities of ~200 fibers from each muscle were determined on digitized images of the stained sections. Tissue sections were digitized as grayscale images, and the value of the SDH staining intensity was expressed as an optical density (OD) value on the above-mentioned image processing system [15, 17, 19]. Each pixel was quantified as one of 256 gray levels. A gray value of zero was equivalent to 100% transmission of light, and that of 255 was equivalent to 0% transmission. The OD units of all pixels within the muscle fiber were converted to a mean OD unit using a calibration photographic tablet which has 21 steps of gradient density ranges and their diffused density values.
Fig. 1. Body weights, and soleus and plantaris muscle weights in 5-, 9-, and 21-week-old LETO and OLETF rats. Values are mean±SD (n=6 for 5 and 9 weeks and n=7 for 21 weeks). ***p<0.001 compared with value of the age-matched LETO group.

Fig. 2. Fiber type distributions of the soleus (A–C) and plantaris (D–F) muscles in 5- (A and D), 9- (B and E), and 21-week-old (C and F) LETO and OLETF rats. Values are mean±SD (n=6 for 5 and 9 weeks and n=7 for 21 weeks). *p<0.05, **p<0.01, ***p<0.001 compared with value of the age-matched LETO group.
Fig. 3
Table 1. Fiber cross-sectional areas of the soleus and plantaris muscles in LETO and OLETF rats at different ages

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Time</th>
<th>LETO</th>
<th>OLETF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soleus</td>
<td></td>
<td>type I</td>
<td>type IIA</td>
</tr>
<tr>
<td>LETO</td>
<td>5 weeks</td>
<td>6</td>
<td>1029±48</td>
</tr>
<tr>
<td></td>
<td>9 weeks</td>
<td>6</td>
<td>1729±37</td>
</tr>
<tr>
<td></td>
<td>21 weeks</td>
<td>7</td>
<td>3147±84</td>
</tr>
<tr>
<td>OLETF</td>
<td>5 weeks</td>
<td>6</td>
<td>1010±30</td>
</tr>
<tr>
<td></td>
<td>9 weeks</td>
<td>6</td>
<td>1755±43</td>
</tr>
<tr>
<td></td>
<td>21 weeks</td>
<td>7</td>
<td>3140±91</td>
</tr>
<tr>
<td>Plantaris</td>
<td></td>
<td>type I</td>
<td>type IIA</td>
</tr>
<tr>
<td>LETO</td>
<td>5 weeks</td>
<td>6</td>
<td>894±41</td>
</tr>
<tr>
<td></td>
<td>9 weeks</td>
<td>6</td>
<td>1661±58</td>
</tr>
<tr>
<td></td>
<td>21 weeks</td>
<td>7</td>
<td>1853±44</td>
</tr>
<tr>
<td>OLETF</td>
<td>5 weeks</td>
<td>6</td>
<td>918±36</td>
</tr>
<tr>
<td></td>
<td>9 weeks</td>
<td>6</td>
<td>1708±56</td>
</tr>
<tr>
<td></td>
<td>21 weeks</td>
<td>7</td>
<td>1943±43</td>
</tr>
</tbody>
</table>

Values are mean±SD (μm²). n, number of animals analyzed.

**Electrophoresis**

The right soleus muscle was used for the analysis of the myosin heavy chain (MHC) isoform component by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) [18]. The muscle was homogenized using a glass homogenizer in 40 vol of homogenizing buffer containing 5 M urea, 2 M thiourea, 0.13% 2-mercaptoethanol, and 10 mM sodium diphosphate decahydrate. The homogenate was mixed with 74 vol of SDS-sample buffer containing 250 mM Tris-HCl (pH 6.8), 2% SDS, 10% glycerol, 5% 2-mercaptoethanol, and 0.02% bromophenol blue. The same sample volume (20 μl) was subjected to SDS-PAGE in a separating gel containing a linear gradient of 5–8% acrylamide and 30–40% glycerol for 24 hr at 4°C. The stacking gel contained 3.5% acrylamide and 35% glycerol. The gel was then silver-stained, and the amounts of the MHC isoforms were estimated by densitometry.

**Measurement of serum level of glucose and insulin**

Sera obtained by centrifugation were used for the measurements of glucose and immunoreactive insulin. Serum glucose was measured by the glucose-oxidase method [28]. Immunoreactive insulin was determined by a radioimmunoassay using the polyethylene glycol method with rat insul-

**Statistics**

Mean and standard deviations (SD) were calculated from individual values using standard procedures. All statistical analyses were performed using the StatView software. A two-way analysis of variance (ANOVA) was used to evaluate the influence of age and group. When the main effects or the interactions between age and group were significant based on the ANOVA analyses, further comparisons between means were made using Scheffé’s post hoc tests.

### III. Results

**Body weight**

The body weight in both the LETO and OLETF groups increased with postnatal growth (Fig. 1). There was no significant difference in the body weight between the 5-week-old LETO and age-matched OLETF groups, while the body weights of the 9- and 21-week-old OLETF groups were significantly greater than those of the age-matched LETO groups.

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Fig. 3. Serial transverse sections of the soleus muscle of 5-week-old LETO (A–D) and OLETF (E–H) rats stained for ATPase and succinate dehydrogenase (SDH) activities. A and E: ATPase following preincubation at pH 10.4. B and F: ATPase following preincubation at pH 4.5. C and G: ATPase following preincubation at pH 4.3. D and H: SDH activity; 1, type I; 2, type IIA; 3, type IIC. Bar=50 μm.

Fig. 4. Serial transverse sections of the soleus muscle of 9-week-old LETO (A–D) and OLETF (E–H) rats stained for ATPase and succinate dehydrogenase (SDH) activities. A and E: ATPase following preincubation at pH 10.4. B and F: ATPase following preincubation at pH 4.5. C and G: ATPase following preincubation at pH 4.3. D and H: SDH activity; 1, type I; 2, type IIA; 3, type IIC. Bar=50 μm.

Fig. 5. Serial transverse sections of the soleus muscle of 21-week-old LETO (A–D) and OLETF (E–H) rats stained for ATPase and succinate dehydrogenase (SDH) activities. A and E: ATPase following preincubation at pH 10.4. B and F: ATPase following preincubation at pH 4.5. C and G: ATPase following preincubation at pH 4.3. D and H: SDH activity; 1, type I; 2, type IIA. Bar=50 μm.
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Muscle weight

The soleus and plantaris muscle weights in both the LETO and OLETF groups increased with postnatal growth (Fig. 1). There was no significant difference in the soleus or plantaris muscle weight between the LETO and age-matched OLETF groups, irrespective of their ages.

Total fiber number

The total fiber numbers on the entire cross-section of the soleus muscle in the 5-, 9-, and 21-week-old LETO groups were 2362±292, 2388±60, and 2382±67, respectively, while those of the 5-, 9-, and 21-week-old OLETF groups were 2372±90, 2395±54, and 2356±52, respectively. There were no significant differences in the total fiber number of the soleus muscle among these groups.

Fiber type distribution

There was no significant difference in the fiber type distribution of the soleus and plantaris muscle between the 5-week-old LETO and age-matched OLETF groups (Figs. 2, 3). In contrast, a higher percentage of type I fibers was observed in the soleus muscle of the 9-week-old OLETF group than in that of the age-matched LETO group (Figs. 2, 4). In addition, there were no type IIA fibers in the soleus muscles of the 9- and 21-week-old OLETF groups (Figs. 2, 5). A lower percentage of type I fibers was observed in the plantaris muscle of the 9-week-old OLETF group than in that of the age-matched LETO group (Fig. 2). In addition, a lower percentage of type IIA fibers and a higher percentage of type IIB fibers were observed in the plantaris muscles of the 9- and 21-week-old OLETF groups than in those of the age-matched LETO group (Fig. 2). There were no type I fibers in the plantaris muscle of the 21-week-old OLETF group (Fig. 2).

Fiber cross-sectional area

There was no significant difference in the fiber cross-sectional area of the soleus or plantaris muscle between the LETO and age-matched OLETF groups, irrespective of their ages (Table 1).

Fiber SDH activity

There was no significant difference in the SDH activity of fibers in the soleus or plantaris muscle between the LETO and age-matched OLETF groups, irrespective of their ages (Table 2).

MHC isof orm component

The MHC isoforms in the soleus muscle were classified as MHC I and MHC IIA according to their molecular weights. The MHC I isof orm increased and the MHC IIA isof orm decreased with postnatal growth in both the LETO and OLETF groups (Fig. 6). There was no significant difference in the MHC isof orm component of the soleus muscle between the 5-week-old LETO and age-matched OLETF groups. In contrast, a higher percentage of MHC I isof orm and a lower percentage of MHC IIA isof orm were observed in the soleus muscle of the 9-week-old OLETF group compared with the age-matched LETO group. There was no MHC IIA isof orm in the soleus muscle of the 21-week-old OLETF group.

Serum glucose and insulin level

The serum glucose and insulin concentrations in the OLETF group increased with postnatal growth (Fig. 7). There was no significant difference in the serum glucose or insulin concentration between the 5-week-old LETO and age-matched OLETF groups. In contrast, the serum glucose and insulin concentrations of the 9- and 21-week-old

| Table 2. Fiber succinate dehydrogenase activities of the soleus and plantaris muscles in LETO and OLETF rats at different ages |
|----------------|---------|---------|---------|
|                | Soleus  |         |         |
| n              | type I  | type IIA | type IIC |
| LETO 5 weeks   | 6       | 0.54±0.03| 0.67±0.03| 0.61±0.03|
| 9 weeks        | 6       | 0.54±0.03| 0.73±0.03| 0.67±0.03|
| 21 weeks       | 7       | 0.52±0.02| 0.72±0.04|           |
| OLETF 5 weeks  | 6       | 0.54±0.03| 0.66±0.02| 0.63±0.02|
| 9 weeks        | 6       | 0.53±0.02| 0.64±0.04|           |
| 21 weeks       | 7       | 0.51±0.02|           |           |
| Plantaris n    | type I  | type IIA | type IIB |
| LETO 5 weeks   | 6       | 0.73±0.02| 0.78±0.03| 0.43±0.02|
| 9 weeks        | 6       | 0.72±0.02| 0.78±0.02| 0.42±0.02|
| 21 weeks       | 7       | 0.71±0.02| 0.78±0.02| 0.44±0.04|
| OLETF 5 weeks  | 6       | 0.74±0.02| 0.78±0.02| 0.39±0.04|
| 9 weeks        | 6       | 0.73±0.03| 0.79±0.02| 0.41±0.04|
| 21 weeks       | 7       | 0.78±0.02| 0.78±0.02| 0.42±0.04|

Values are mean±SD. Data are shown as optical density as described in Materials and Methods. n, number of animals analyzed.
OLETF groups were significantly greater than those of the age-matched LETO groups.

Relationship between fiber type and insulin level
There were no LETO rats with a serum insulin concentration of more than 20 ng/ml, irrespective of their ages (Fig. 8). In contrast, three 9-week-old and all 20-week-old OLETF rats showed serum insulin concentrations of more than 20 ng/ml. These rats had higher percentages of type I fibers, and there were no type IIA fibers remaining.

IV. Discussion
Mammalian skeletal muscles are composed of heterogeneous types of fibers according to their different contractile and/or metabolic properties [3, 4, 34]. Based on enzyme- and immuno-histochemical analyses, skeletal muscle fibers are classified into two major types: slow-twitch type I containing type I MHC isoform and fast-twitch type II containing type II MHC isoform [3, 4, 14]. Additionally, type II fibers have been further classified into type IIA, type IIB, and type IIC fibers, which contain type IIA, type IIB, and both type IIa and type IIb MHC isoforms, respectively [3, 4, 14].

The metabolic properties of muscle fibers also differ among fiber types [12, 30, 31]. The oxidative enzyme activity is higher in type IIA fibers than in type I fibers of the rat slow skeletal muscle, while the oxidative enzyme activity is higher in type I and type IIA fibers than in type IIB fibers of the rat fast skeletal muscle. Slow skeletal muscles are comprised predominantly of high-oxidative type I and/or type IIA fibers, whereas fast skeletal muscles are comprised predominantly of low-oxidative type IIB fibers. Type IIC fibers are exclusively found in the rat soleus muscle during postnatal growth.

Muscle characteristics including fiber type and oxidative capacity may be linked to alterations in insulin action; a high percentage of high-oxidative fibers and an increased oxidative capacity of fibers would be directly related to insulin sensitivity and leanness. Previous studies have shown that patients with type 2 diabetes mellitus [11, 27] as well as subjects with obesity and insulin resistance [25, 26, 33] have a high percentage of type IIB fibers and a low percentage of type I fibers in the vastus lateralis and rectus abdominis muscles, although other studies [7, 22, 32] reported that patients with type 2 diabetes mellitus showed no alterations in the fiber type distribution of the gastrocnemius and vastus...
lateralis muscles. In addition, a previous study [1] observed that the gastrocnemius muscle in obesity-prone rats has a higher percentage of type II fibers than that in non-obese (obesity resistant) controls. Therefore, it is suggested that an increased percentage of glycolytic type II fibers and a decreased percentage of oxidative type I fibers in skeletal muscle are associated with insulin resistance and/or obesity.

Although previous studies [1, 7, 11, 22, 25–27, 32, 33] have examined the fiber type distribution in the fast skeletal muscles of subjects and animals with diabetes and/or obesity, there are few studies available regarding the fiber type distribution in the slow skeletal muscles. Possible changes in the fiber type distribution could have been more evident in slow skeletal muscles, where the proportion of high-oxidative fibers is higher, because high-oxidative fibers have a higher oxidative capacity for carbohydrate and lipid fuel and a greater insulin sensitivity and are characterized by increased fatty acid oxidation, increased triglyceride storage, and low glycolytic capacity compared with low-oxidative fibers [13, 20, 35]. Therefore, the fiber type distribution of the slow soleus muscle in insulin-resistant diabetic rats was examined in the present study. We observed a progressive decline in the percentage of high-oxidative type IIA fibers in the soleus muscle of the OLETF rats during postnatal growth and a complete loss of type IIA fibers in the muscle at 9 and 21 weeks of age (Fig. 2). These findings are consistent with the result using electrophoresis that the percentage of MHC IIA isoform in the soleus muscle of the OLETF rats decreased at 9 weeks of age and that there was no MHC IIA isoform in the muscle at 21 weeks of age (Fig. 6).

We demonstrated that the serum insulin concentration is correlated with the fiber type distribution in the soleus muscle. It is of interest to note that three 9-week-old and all 21-week-old OLETF rats, which had serum insulin concen-
trations over 20 ng/ml, showed higher percentages of type I fibers, and there were no type IIA fibers remaining (Fig. 8).

In the fast plantaris muscle of the OLETF rats, a lower percentage of type I fibers was observed in the 9-week-old OLETF rats, and there were no type I fibers in the 21-week-old OLETF rats. In addition, a higher percentage of low-oxidative type IIB fibers was observed in the 9- and 21-week-old OLETF rats. The high percentage of type IIB fibers in the plantaris muscle observed in the present study is consistent with previous studies using fast skeletal muscles in diabetic patients or animal models of diabetes and/or obesity [1, 11, 27, 33]. It is suggested that alterations in fiber type distribution and oxidative capacity in skeletal muscles play a central role in the development of insulin resistance and/or obesity, since these properties relate to energy production and glucose disposal.

Muscle fiber type appears to be largely genetically determined [11, 24]. It is suggested that the impairment of insulin sensitivity in the OLETF rats is induced by the low percentage of high-oxidative fibers in the skeletal muscle. This means that abnormalities in the muscle fiber type distribution under insulin resistant conditions are the primary factor for hyperinsulinemia. Therefore, it is possible that changes in the muscle fiber type distribution and/or in the capillary density with postnatal growth in skeletal muscles of the OLETF rats result in the development of insulin resistance [10].

It is concluded that the skeletal muscle of OLETF rats is itself insulin resistant, and that fiber type abnormality in the skeletal muscle is associated with impairments of insulin sensitivity and responsiveness; OLETF rats, which had serum insulin concentrations over 20 ng/ml, showed no high-sensitivity and responsiveness; OLETF rats, which had the skeletal muscle is associated with impairments of insulin sensitivity in the OLETF rats and there were no type I fibers in the 21-week-old OLETF rats. It is suggested that changes in the muscle fiber type distribution and oxidative type IIB fibers in the soleus muscle. It is suggested that alterations in fiber type distribution and oxidative capacity in skeletal muscles play a central role in the development of insulin resistance and/or obesity, since these properties relate to energy production and glucose disposal.

Muscle fiber type appears to be largely genetically determined [11, 24]. It is suggested that the impairment of insulin sensitivity in the OLETF rats is induced by the low percentage of high-oxidative fibers in the skeletal muscle. This means that abnormalities in the muscle fiber type distribution under insulin resistant conditions are the primary factor for hyperinsulinemia. Therefore, it is possible that changes in the muscle fiber type distribution and oxidative type IIB fibers in the soleus muscle. It is suggested that abnormalities in the muscle fiber type distribution are the primary factor for hyperinsulinemia.

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VI. References


