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## Muscle Fiber Changes of the Vastus Medialis in Rheumatoid Patients

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## Abstract

To study the pathology of muscle atrophy in rheumatoid arthritis (RA), we examined the vastus medialis in rheumatoid patients histologically. The relationship of the findings to their ambulatory ability and long-term steroid therapy was investigated. The muscles of the RA patients were also compared with those of patients with osteoarthritis (OA). Specimens of the vastus medialis were collected from 29 knees of 23 patients with RA and 16 knees of 13 patients with OA during total knee arthroplasty. Muscle fibers were classified according to their type, and the ratio between the area of single type I and type II fibers as well as the ratio between the total area of these fibers was calculated. The total area of type II fibers in the RA group was significantly greater than in the OA group ( $P < 0.05$ ). In the RA group, the mean proportion of the type II fibers relative to the total muscle fiber area tended to increase with the decline of ambulatory ability, while there was no such increase in the OA group. The proportion of type II fibers was increased significantly in RA patients on long-term steroid therapy when compared to those without therapy. In the ratio of the area of a single fiber, there was no clear relationship to ambulatory ability and long-term steroid therapy. It is considered that muscle atrophy in RA is not solely disuse atrophy, but also has a close relationship to steroid therapy and the pathology of the disease itself.

**KEYWORDS:** muscle atrophy, muscle fiber type, vastus medialis, rheumatoid arthritis

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## Muscle Fiber Changes of the Vastus Medialis in Rheumatoid Patients

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To study the pathology of muscle atrophy in rheumatoid arthritis (RA), we examined the vastus medialis in rheumatoid patients histologically. The relationship of the findings to their ambulatory ability and long-term steroid therapy was investigated. The muscles of the RA patients were also compared with those of patients with osteoarthritis (OA). Specimens of the vastus medialis were collected from 29 knees of 23 patients with RA and 16 knees of 13 patients with OA during total knee arthroplasty. Muscle fibers were classified according to their type, and the ratio between the area of single type I and type II fibers as well as the ratio between the total area of these fibers was calculated. The total area of type II fibers in the RA group was significantly greater than in the OA group ( $P < 0.05$ ). In the RA group, the mean proportion of the type II fibers relative to the total muscle fiber area tended to increase with the decline of ambulatory ability, while there was no such increase in the OA group. The proportion of type II fibers was increased significantly in RA patients on long-term steroid therapy when compared to those without therapy. In the ratio of the area of a single fiber, there was no clear relationship to ambulatory ability and long-term steroid therapy. It is considered that muscle atrophy in RA is not solely disuse atrophy, but also has a close relationship to steroid therapy and the pathology of the disease itself.

**Key words:** muscle atrophy, muscle fiber type, vastus medialis, rheumatoid arthritis

**I**n rheumatoid arthritis (RA), skeletal muscle atrophy is common. Paget (1) reported that muscle atrophy related to articular inflammation was more severe and

developed more rapidly than that induced by disuse alone. Subsequently, De Andrade (2) reported that there were both quantitative and qualitative differences between muscle atrophy in experimental arthritis and that induced by articular immobilization in cats. There have been a number of reports on the pathology of disuse muscle atrophy, but there is no consensus on the type of muscle fibers primarily affected in disuse atrophy. Although histologic examination of RA skeletal muscles has revealed predominant atrophy of type II fibers (3), such a finding is not specific to RA and is also observed in disuse atrophy and other pathological conditions. Brooke and Kaplan (4) classified biopsy specimens of the biceps brachii in RA patients pathologically by disease stage (stages I-IV). Type II and I fibers clearly showed atrophy in mild RA (stages I/II) and severe RA (stage III), respectively. Magyar *et al.* (3) performed a histochemical study of muscle biopsy specimens in RA patients, and noted that type II fibers were thin and atrophic while type I fibers were within normal limits. A Japanese study (5) that compared the vastus medialis in RA patients, patients with osteoarthritis (OA), and normal individuals, found a decrease of type I/IIA fibers and an increase of type IIB/IIC fibers in the RA group. The cross-sectional area of all types of muscle fibers was also smaller in the RA group than in the other two groups.

However, in addition to disuse, steroid therapy is thought to contribute to the muscle atrophy that develops in RA. In this study, histologic examination of the vastus medialis was performed in RA patients to investigate the relationship of the findings to their ambulatory ability as well as long-term steroid therapy, and a comparison was also made with the vastus medialis in OA patients.

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## Subjects and Methods

**Subjects.** The subjects included 23 patients (29 knees) with RA aged 47–80 years (mean: 63.2 years), who were diagnosed according to the criteria of the American Rheumatism Association (6). Thirteen patients (16 knees) with OA aged 53–83 years (mean: 70.9 years) were also studied. Nine RA patients (10 knees) had been treated with corticosteroids for at least 6 months or more.

**Methods.** The ambulatory ability of the RA and OA patients was evaluated according to Fujibayashi's classification (7) as shown in Table 1.

Samples (about 1 cm<sup>3</sup>) of the vastus medialis were collected at the time of total knee arthroplasty and frozen at –80°C. The specimens were then cut into 10 μm sections with a cryostat (Tissue-Tek, Bayer Corporation) and subjected to ATPase staining (pH 4.2–4.6, 10.3–10.9) (8). Muscle fibers were classified into types I and II according to their staining (pH 10.3–10.9) properties and the cross-sectional area of about 200 muscle fibers per specimen was determined using an automatic image analyzer (Osteomorphometer System, System Supply). The ratio of the total area of type II fibers to that of type I fibers (TAII/I ratio) and the ratio of the area of a single type II fiber to that of a single type I fiber (SAII/I ratio) were calculated. We used the *t*-test to analyze the data statistically.

The following studies were performed using the

TAII/I and SAII/I ratio data: a) comparison between the RA and OA groups, b) investigation of the relationship between fiber distribution and ambulatory ability in the RA and OA groups, and c) investigation of the influence of long-term steroid therapy in the RA group.

## Results

**Comparison between the RA and OA groups.** The TAII/I ratio was  $1.88 \pm 1.57$  in the RA group, and  $0.94 \pm 0.38$  in the OA group. The proportion of type II fibers was significantly greater in the RA group ( $P < 0.05$ ). The value of this ratio varied widely in the RA group when compared with the OA group (Fig. 1-a).

Although there was no significant difference in the SAII/I ratio between the groups, the cross-sectional area of a single type II fiber was smaller than that of a single type I fiber in both groups (Fig. 1-b).

**Relationship between fiber distribution and ambulatory ability (Table 2).** ATPase staining of the normal vastus medialis indicated that the ratio of the cross-sectional area of a single type I fiber to that of a single type II fiber was approximately 1:1, and there were no variations in the size of either type of fiber.

Among patients with a class 3b ambulatory ability, the TAII/I ratio was  $0.998 \pm 0.774$  for the RA group and  $1.056 \pm 0.208$  for the OA group. Thus, the ratio was approximately 1:1. The SAII/I ratio was  $0.724 \pm 0.321$  and  $0.537 \pm 0.115$  in the RA and OA groups, respective-

**Table 1** Classification by ambulatory ability

Class	Ambulatory ability	RA		OA	
		Cases <sup>a</sup>	Knees <sup>b</sup>	Cases <sup>a</sup>	Knees <sup>b</sup>
3a	The ability to stand up unaided, descending/ascending stairs, and walk for 0.5–1 km	0	0	0	0
3b	The ability to stand up with the aid of a cane, descend/ascend stairs, and walk for 0.5–1 km	4	4	3	3
3c	The ability to walk outdoors	5	6	7	8
3d	The ability to walk indoors	9	11	3	5
4	Inability to walk	5	8	0	0
Total		23	29	13	16

RA: Rheumatoid arthritis, OA: Osteoarthritis.

a: Number of cases, b: Number of knees.

**Table 2** Relationship between fiber distribution and ambulatory ability

Class	TAII/I	SAII/I	
			Class
RA	3b	$0.998 \pm 0.774$	$0.724 \pm 0.321$
	3c	$1.704 \pm 1.614$	$0.611 \pm 0.278$
	3d	$2.054 \pm 1.474$	$0.601 \pm 0.323$
	4	$2.230 \pm 1.967$	$0.759 \pm 0.405$
OA	3b	$1.056 \pm 0.208$	$0.537 \pm 0.115$
	3c	$0.899 \pm 0.487$	$0.681 \pm 0.284$
	3d	$0.925 \pm 0.314$	$0.459 \pm 0.076$

TAII/I: The ratio of the total area of type II fibers to that of type I fibers; SAII/I: The ratio of the area of a single type II fiber to that of a single type I fiber. RA and OA: See legend to Table 1.

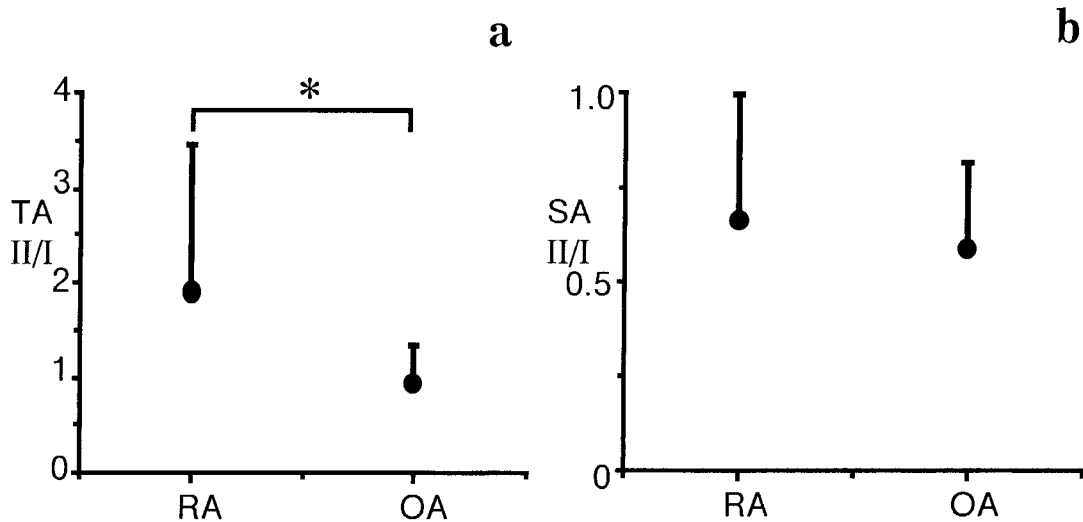


Fig. 1 Comparison between the rheumatoid arthritis (RA) and osteoarthritis (OA) groups. a: The ratio of the total area of type II fibers to that of type I fibers (TAII/I) (\* $P < 0.05$ ), b: The ratio of the area of a single type II fiber to that of a single type I fiber (SAII/I).

ly, so the cross-sectional area of type II fibers was smaller in both groups (Fig. 2-a, b).

Among patients with a class 3c ambulatory ability, the TAII/I ratio was  $1.704 \pm 1.614$  for the RA group and  $0.899 \pm 0.487$  for the OA group. In the RA group, the total area ratio was increased compared with the class 3b patients while it remained nearly 1:1 in the OA group. The SAII/I ratio was  $0.611 \pm 0.278$  and  $0.681 \pm 0.284$  in the RA and OA groups, respectively. Type II fibers showed more variation of size in the RA group (Fig. 2-c, d).

Among patients with class 3d ambulatory ability, the TAII/I ratio was  $2.054 \pm 1.474$  in the RA group and  $0.925 \pm 0.314$  in the OA group. Although the proportion of type II fibers relative to the total muscle fiber area was again increased in the RA group, it remained unchanged from that for classes 3b and 3c in the OA group. Thus, there was no increase in this group despite a decrease in ambulatory ability. The SAII/I ratio was  $0.601 \pm 0.323$  and  $0.459 \pm 0.076$  for the RA and OA groups, respectively. In the RA group, the fibers varied markedly in size compared with the OA group (Fig. 2-e, f).

Class 4 patients were only found in the RA group. The TAII/I ratio was again increased to  $2.230 \pm 1.967$  and type II fibers occupied approximately 70% of the total muscle fiber area. The SAII/I ratio was  $0.759 \pm 0.405$ . Thus, the type II fibers were again smaller in size,

but there was no definite trend with the changes in ambulatory ability (Fig. 2-g).

With regard to the total area ratio, the ratio of type II to type I fibers generally increased in the RA group as ambulatory ability declined, but there was no such increase in the OA group (Fig. 3-a). The area ratio of single fibers showed no definite trends with a decrease of ambulatory ability in both the RA and OA groups (Fig. 3-b).

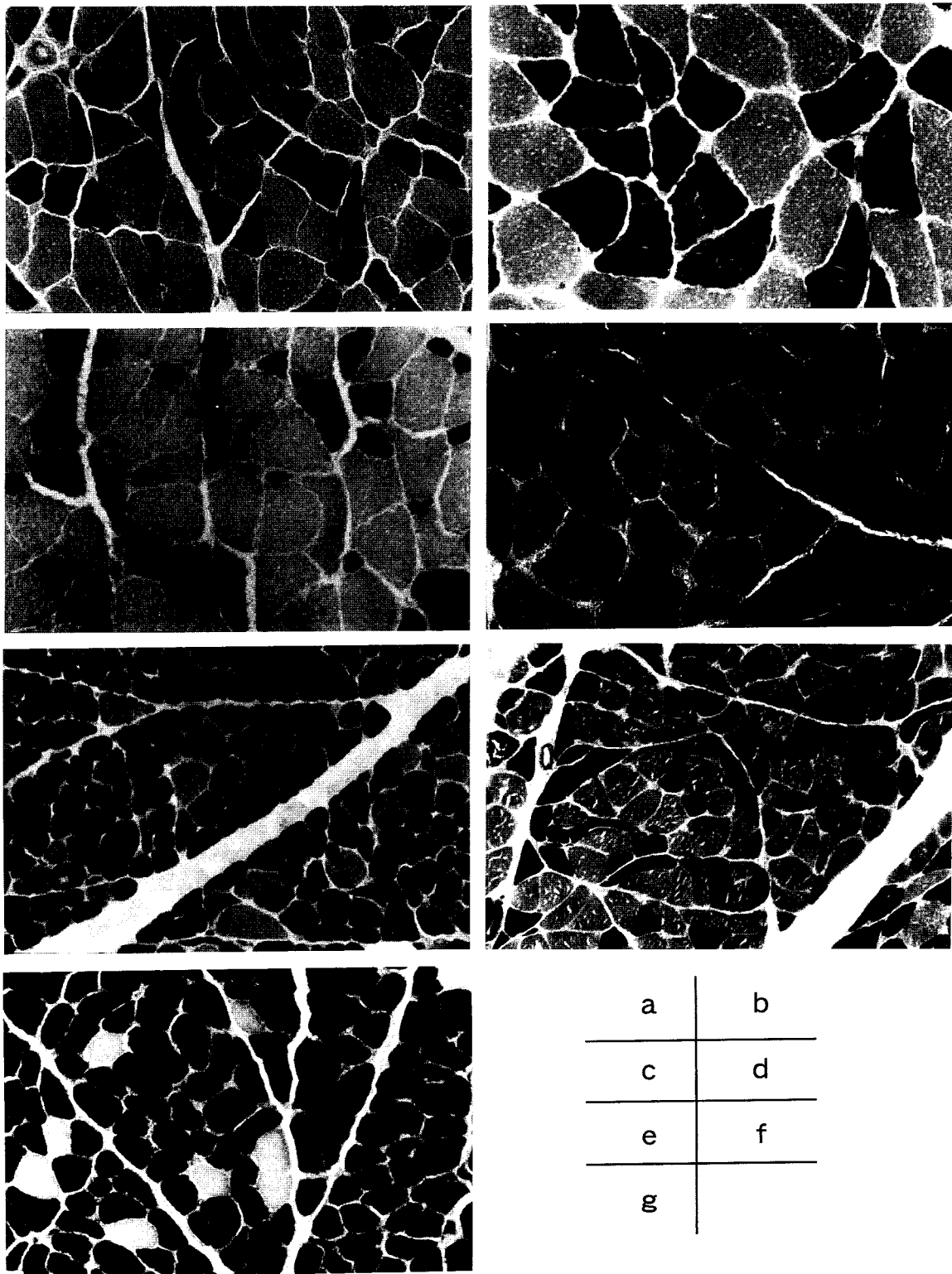
#### ***Influence of long-term steroid therapy.***

The influence of long-term steroid therapy was assessed in the RA group. A history of treatment with prednisolone at a dose of  $\geq 5$  mg for 6 months or more was defined as long-term steroid therapy. Of the 23 patients (29 knees) with RA, 9 patients (10 knees) had received long-term treatment.

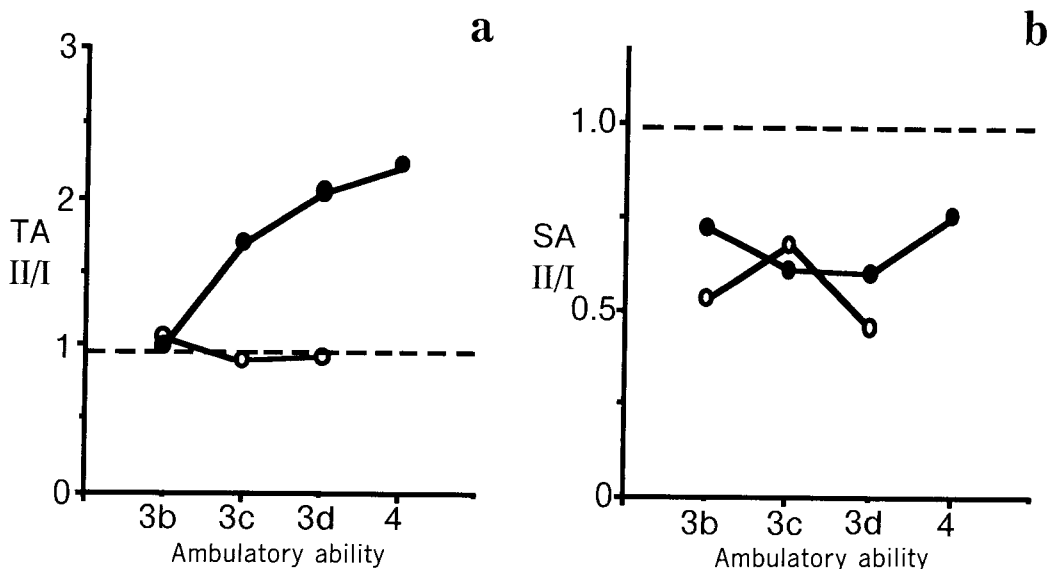
The mean TAII/I ratio was  $2.839 \pm 2.051$  for the patients with long-term therapy and  $1.382 \pm 0.970$  for those who had not received it, with the difference between the two groups being significant ( $P < 0.05$ ) (Fig. 4-a).

The mean SAII/I ratio was  $0.825 \pm 0.373$  and  $0.579 \pm 0.279$  for the patients with and without long-term steroid therapy, respectively (Fig. 4-b).

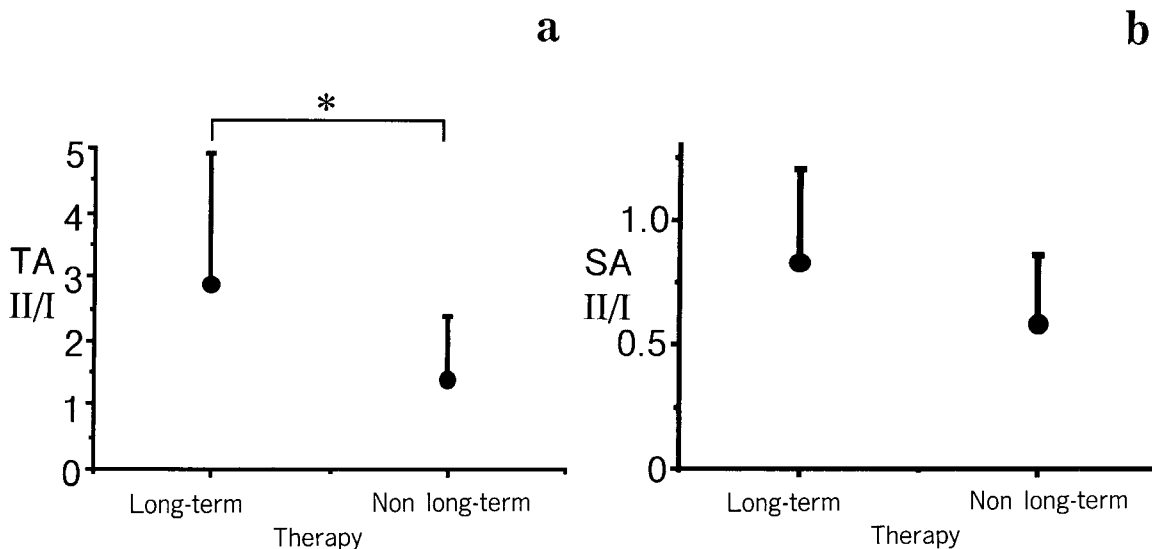
A comparison was also made after stratification for each ambulatory ability class, although the number of specimens was limited. The mean TAII/I ratio was 0.573, 1.09, 1.85, and 1.18 for classes 3b, 3c, 3d, and



**Fig. 2** ATPase staining of the vastus medialis of the patients with RA and OA. **a, b:** Ambulatory ability. Class 3b (**a:** RA,  $\times 200$ , pH 10.8; **b:** OA,  $\times 200$ , pH 10.9); **c, d:** Class 3c (**c:** RA,  $\times 200$ , pH 10.7; **d:** OA,  $\times 200$ , pH 10.8); **e, f:** Class 3d (**e:** RA,  $\times 100$ , pH 10.7; **f:** OA,  $\times 100$ , pH 10.9); and **g:** Class 4 (RA,  $\times 100$ , pH 10.8). RA and OA: See legend to Fig. 1.



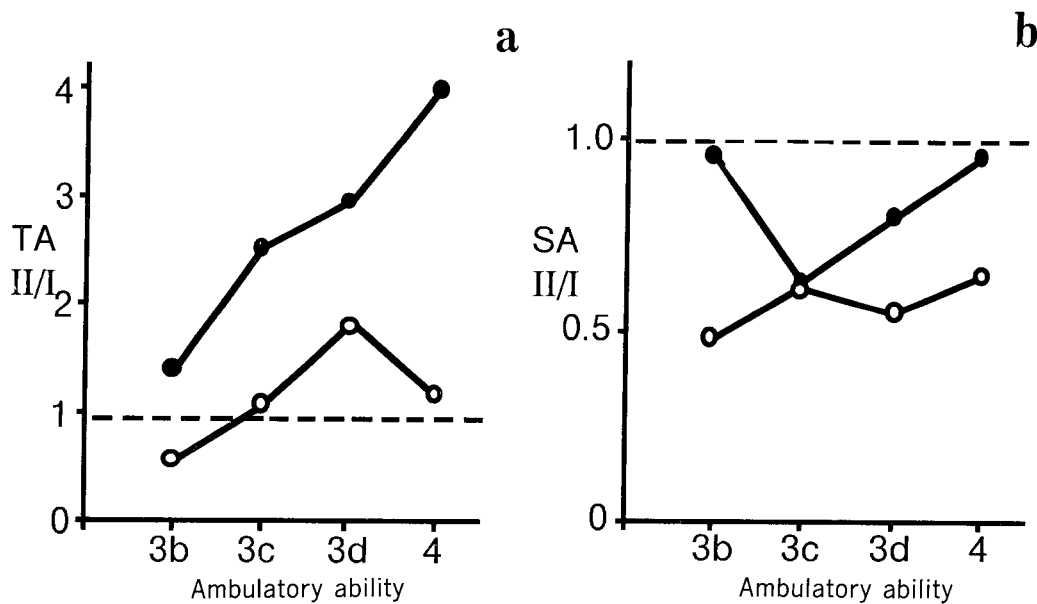
**Fig. 3** Relationship between fiber distribution and ambulatory ability. Comparison between the RA and OA groups. **a:** The ratio of the total area of type II fiber to that of type I fiber (TAII/I), **b:** The ratio of the area of a single type II fiber to that of a single type I fiber (SAII/I). The distribution of muscle fiber types in the vastus lateralis of normal individuals was calculated according to the method of Larsson *et al.* to provide normal control data. (●): RA, (○): OA, and (···): Normal. RA and OA: See legend to Fig. 1.



**Fig. 4** Influence of long-term steroid therapy. **a:** TAII/I (\*  $P < 0.05$ ), and **b:** SAII/I. TAII/I: The ratio of the total area of type II fiber to that of type I fiber; SAII/I: The ratio of the area of a single type II fiber to that of a single type I fiber.

4 in the patients without long-term steroid therapy respectively, showing a trend for type II fibers to increase. In

the patients receiving long-term steroid therapy, the mean TAII/I ratio was 1.42, 2.53, 2.99, and 3.98, respective-



**Fig. 5** Relationship between fiber distribution and ambulatory ability; Influence of long-term steroid therapy. **a:** TAI/1, and **b:** SAI/1. TAI/1, SAI/1 and RA: See legends to Figs. 1, 2, 3. (●): RA patients with steroid treatment, (○): RA patients without steroid treatment, and (---): Normal.

ly. Type II fibers increased markedly as the ambulatory ability declined, and the extent of the increase was related to the decrease in ability (Fig. 5-a).

In contrast, no definite trend of the mean SAI/1 ratio was noted with a decrease in the ambulatory ability (Fig. 5-b).

## Discussion

There have been a number of reports on the muscle fiber changes in disuse muscle atrophy (9-12). McDougall *et al.* (9) investigated the effect of immobilization in humans and found that type II fibers primarily underwent atrophy. According to Appell (10), however, it is the type I fibers which principally undergo atrophy with disuse in both humans and animals. Haggmark *et al.* (11) performed muscle biopsy preoperatively and at the time of postoperative cast application in patients with knee ligament injuries, and reported that most of the reduction in the cross-sectional area was due to a reduction of type I fibers. A biopsy study of the vastus medialis was done before and after operation in patients undergoing knee joint surgery, and a decrease in the proportion of type I

fibers as well as an increase in type II fibers were noted (12). Thus, there is no general agreement regarding the type of muscle fibers principally affected in disuse muscle atrophy, but reports stating that type I fibers are more markedly reduced appear to predominate.

Histologic examinations of RA skeletal muscles has previously revealed the predominant atrophy of type II fibers (3). However, this finding is not specific to RA and is also observed in disuse atrophy and other pathologic conditions. Brooke and Kaplan (4) performed biopsy of the biceps brachii in RA patients, and classified the pathological findings by disease stage according to the American Rheumatism Association criteria (13). They stated that type I and II fibers showed atrophy in mild RA (stages I and II) and severe RA (stage III), respectively. However, the present study using a classification of ambulatory ability showed that only type II fibers became atrophic with a decrease in ability. This discrepancy may be attributable to differences between the biceps brachii and the vastus medialis or to differences in the method of classifying the severity of RA and the ambulatory ability. Magyar *et al.* (3) performed muscle biopsy in 100 RA patients (sampling the vastus medialis in 29) and examined



the specimens to histochemically. They stated that type II fibers were thin and atrophic, while type I fibers remained within normal limits. Sano *et al.* (5) compared the vastus medialis in 13 RA patients with that in 12 OA patients and 5 normal individuals. The proportion of type I and IIA fibers was smaller and that of type IIB and IIC fibers was larger in the RA patients than in the normal control group. They also found that the cross-sectional area of the muscle fibers was smaller in the RA group than in the other two groups. However, since steroid therapy as well as disuse may contribute to muscle atrophy in RA, these patients should not be considered to be a homogeneous population. When no division was made into therapeutic subtypes in the present study, we found that the relative type II fiber area increased markedly in the RA group as the ambulatory ability declined, a finding similar to that observed in disuse muscle atrophy. The absence of an increase in the ratio of the total type II fiber area in the OA group suggests that muscle atrophy in RA differs from simple disuse muscle atrophy. When long-term steroid therapy was also considered, the proportion of type II fibers was significantly larger in the patients on therapy. Although type II fibers also tended to increase in the patients without long-term steroid therapy, they increased markedly in the patients on therapy as the ambulatory ability declined, and the extent of this increase was related to the decrease in ambulation. Thus, the increased proportion of type II fibers with a decrease of ambulatory ability in the RA group may also be related to long-term steroid therapy.

Selective atrophy of type II fibers is generally thought to be secondary to disuse atrophy and arthrosis or to develop in steroid myopathy (14). Our study showed no definite tendency for the ratio of the cross-sectional area of a single type II and type I fibers to decrease along with a decline in the ambulatory ability, but type II fibers were smaller in both in the RA and OA groups. In the RA group, the type II/I area ratio varied widely and the muscle fibers tended to vary in size. Satoyoshi *et al.* (15) examined the quadriceps femoris in patients with Cushing's syndrome and steroid myopathy, and noted that type II fibers were smaller than type I fibers. In the present study, determination of the ratio of the cross-sectional fiber area indicated that type II fibers showed less atrophy in the patients on long-term steroid therapy than in those without such therapy, but these fibers were still atrophic when compared with type I fibers regardless of the presence or absence of long-term steroid therapy.

Since it was difficult to collect specimens of the vastus medialis from normal individuals, the distribution of muscle fiber types in the vastus lateralis of normal individuals was calculated according to the method of Larsson *et al.* (16) to provide normal control data (Fig. 3). In the RA group, the TAI/II ratio was larger than normal for class 3b and 3c patients, and was further increased to about 2.5-fold above normal in the class 3d and 4 patients. In the OA group, however, there was no such increase. In contrast, the SAI/II ratio was smaller than normal in patients of all classes from both the RA and OA groups.

The present results suggest that the muscle fiber changes in the vastus medialis of RA patients were not simply due to disuse atrophy, but that they were also related to steroid therapy and the pathology of RA itself. The increase in the proportion of type II fibers and the decrease of type I fibers along with the decline of ambulatory ability in the RA group implies that type I fibers were transformed into type II fibers. However, because we did not subdivide type II fibers into subtypes (IIA, IIB, IIC) in the present investigation, it is unclear whether the proportion of type II fibers increased through undifferentiated type IIC fibers (17, 18). Furthermore, it is doubtful whether the new type II fibers thus formed had the characteristics of normal type II fibers.

In conclusion, the relationships between the distribution of muscle fiber types in the vastus medialis of RA patients and their ambulatory ability as well as long-term steroid therapy was investigated. Comparison was also made with OA patients, and the following information was obtained.

In the RA group, the proportion of type II fibers tended to increase as the ambulatory ability declined, while there was no such increase in the OA group. The total area of type II fibers was larger in the patients on long-term steroid therapy than in those without therapy, and it increased markedly with a decline in the ambulatory ability in the RA group.

The area of a single type II fiber was smaller than that of a type I fiber in both the RA and OA groups, and the fibers varied in size.

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