Aging of skeletal muscle: a 12-yr longitudinal study

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**Frontera, Walter R., Virginia A. Hughes, Roger A.
Fielding, Maria A. Fiatarone, William J. Evans, and
Ronenn Roubenoff.** Aging of skeletal muscle: a 12-yr
longitudinal study. *J Appl Physiol* 88: 1321–1326, 2000.—
The present study examines age-related changes in skeletal
muscle size and function after 12 yr. Twelve healthy seden-
tary men were studied in 1985–86 (T1) and nine (initial mean
age 65.4 $\pm$ 4.2 yr) were reevaluated in 1997–98 (T2). Iso-
kinetic muscle strength of the knee and elbow extensors and
flexors showed losses ($P < 0.05$) ranging from 20 to 30% at
slow and fast angular velocities. Computerized tomography
($n = 7$) showed reductions ($P < 0.05$) in the cross-sectional
area (CSA) of the thigh (12.5%), all thigh muscles (14.7%),
quadriceps femoris muscle (16.1%), and flexor muscles (14.9%).
Analysis of covariance showed that strength at T1 and
changes in CSA were independent predictors of strength at
T2. Muscle biopsies taken from vastus lateralis muscles ($n =$
6) showed a reduction in percentage of type I fibers (T1 = 60%
vs. T2 = 42%) with no change in mean area in either fiber
type. The capillary-to-fiber ratio was significantly lower at T2
(1.39 vs. 1.08; $P = 0.043$). Our observations suggest that a
quantitative loss in muscle CSA is a major contributor to the
decrease in muscle strength seen with advancing age and,
together with muscle strength at T1, accounts for 90% of the
variability in strength at T2.

sarcopenia; muscle strength; muscle size; muscle fiber type
and area

CROSS-SECTIONAL STUDIES HAVE shown significant reduc-
tions in muscle mass and strength and alterations in
body composition with advancing age (14, 17, 24).
However, the loss of strength over time is larger in
longitudinal studies (6, 9), suggesting that a cross-
sectional study design underestimates age-related
changes in muscle function.

A few longitudinal studies of skeletal muscle strength
have been published. A decline (6, 12, 25–27, 34), no
change (16), and gains in strength (6, 12, 28) have all
been reported in studies of different skeletal muscles

after varying periods of time (4–25 yr). Very few studies
have compared changes in function with alterations in
muscle size and fiber size and type in the same popula-
tion over time (3, 4, 33).

Muscle strength and area of type II muscle fibers
have been reported to decrease with age, whereas no
changes have been observed in capillarization in one
longitudinal study (4). No change in type I or type II
fiber area was reported by Trappe et al. (33) in middle-
aged runners, whereas hypertrophy in both fiber types
has been reported by others (3) in older subjects.
Furthermore, although one study reported no change
in fiber-type distribution (4), a longer follow-up of the
same subjects showed a reduced proportion in type IIB
fibers with no significant change in the prevalence of
type IIA or type I fibers (3). In the study of Trappe et al.
(33), distance runners showed a significant increase in
the proportion of type I fibers. Changes in muscle
cross-sectional area (CSA) were not evaluated in any of
these longitudinal studies. Finally, because different
muscles, age groups, and subjects with varying levels of
physical activity were studied, it is difficult to reach
more definitive conclusions.

Strength of the extensor muscles of the knee is a
predictor of dependency and survival (28, 30, 32). Thus
understanding the basis of dysfunction of that muscle
group in old age has important clinical and social
implications. The purpose of the present study was to
evaluate longitudinal changes in a group of older men
in *1*) strength of the knee and elbow extensors and
flexors, *2*) CSA of the quadriceps muscle, and *3*) fiber-
type distribution, mean fiber area, and capillarization
in vastus lateralis muscle.

MATERIALS AND METHODS

Study design and subjects. The men in the present study
were tested twice ∼12 yr apart. The subjects originally
participated in a strength-conditioning program conducted in
1985–86 (T1) (15). The second evaluation was conducted in
1997–98 (T2). All subjects ($n = 12$) who participated in T1
(only pretraining data were used in the present study) were
invited to participate in T2, and a total of nine agreed (the
sample size for different tests is indicated in the tables). One
had died of lung cancer, and two declined to participate. The

left side (nondominant) was evaluated in all subjects in T1 and T2 except for one subject in which the right side was evaluated at T2 because of an intervening left hip arthroplasty. In that subject, no side-to-side differences were noted in T1 in muscle strength or CSA. Also, changes in quadriceps strength and extensor CSA were similar to those seen in the rest of the group.

The volunteers received a complete explanation of the purposes and procedures and gave their written consent. A comprehensive medical evaluation, including a medical history, physical examination, routine blood and urine tests, and a resting electrocardiogram, was performed before their participation in the study at both time points. In T1, only healthy volunteers without diseases that could alter neuromuscular function and with a normal maximal exercise test were accepted for the study. The level of recreational activity and sports participation over the last year was estimated by using a questionnaire (18). The study was approved by the Human Investigation Review Committee of Tufts University-New England Medical Center.

Muscle strength measurements. An isokinetic dynamometer (Cybex II, Medway, MA) was used to measure strength (N·m) of the knee extensors and flexors at 60 and 240°/s and of the left elbow flexors and extensors at 60 and 180°/s, as previously reported (14). The placement of the lever arm with relation to the subject's leg was carefully controlled. The subjects performed three (five in T2) maximal voluntary contractions at each velocity on 2 testing days (the two tests were made 10–14 days apart at T1 and on consecutive days at T2), and the peak torque was recorded. In addition, the subjects performed 25 maximal contractions at 240°/s, and the area under the curve was used to calculate total work as an index of local muscle endurance.

Computerized tomography (CT). At T1 a CT scan of both thighs was performed halfway between the pubic symphysis and the lower pole of the patella. The scanner was a third-generation Siemens DR3 (Erlanger, Germany) operating at 125 kV peak. Technical factors employed were slice width of 8 mm and a scanning time of 7 s. In T2, the scan of one thigh was obtained in eight subjects at the level of the biopsy scar visible from T1 by using a GE Highspeed Advantage CT scanner (Milwaukee, WI) operating at 100 kV peak and 170 mA. Technical factors were slice width of 10 mm and a scanning time of 1 s. As mentioned previously, for one subject the CT at T2 was obtained in the right thigh at the level of the biopsy in the left leg.

From the CT image, the CSAs (mean of two measurements) occupied by all tissues combined (thigh area), all muscles, quadriceps femoris muscle, and flexors (semimembranosus, semitendinosus, and the short and long heads of the biceps femoris) were measured by using manual planimetry (model 317E, Gebruder Half GMBH). Inter- and intramuscle fat was not quantified separately and is, therefore, included in CSA measurements. The error of the planimetric method, expressed as the coefficient of variation of a single value for a single observer and three measurements, was <1.5% for the various measurements. The test-retest (3 wk apart) reliability for muscle area determined by using image analysis of CT images in two subjects was 0.6% (coefficient of variation). One subject was not included in the analysis of the muscle CSA because of technical errors.

Muscle biopsy. Muscle biopsies were taken from vastus lateralis muscle at the level of the CT scan by using a 5-mm Duchenne biopsy needle (7) and suction (13). The same biopsy site was used on each occasion (T1 and T2), because it was possible to identify the scar of the biopsy at T1 in all subjects. The specimen was mounted in embedding medium (OCT,

Miles Laboratories, Naperville, IL), frozen in isopentane cooled to the temperature of liquid nitrogen, and stored for later sectioning and staining.

For histochemical analysis, serial 10-μm cross sections were cut in a cryostat at −20°C and stained for myofibrillar ATPase at pH 9.4 after preincubation at pH 4.3 (11, 26). The percent distribution of type I and II fibers was calculated. The mean number of fibers counted per biopsy was 408 ± 190 (range 203–712) in T1 and 453 ± 159 (range 303–661) in T2.

Measurements of type I and II fiber area were performed by using manual planimetry by a single investigator unaware of the identity of the specimens. All measurements were done three times, and the average was used for calculation of muscle fiber areas (MFA). Only areas without artifacts and distinct cell borders were measured. The mean number of fibers measured per biopsy was 114 ± 62 (range 57–251) type I and 105 ± 41 (range 39–196) type II fibers in T1 and 99 ± 29 (range 56–143) type I and 145 ± 45 (range 91–194) type II in T2.

Cross sections of the biopsies were stained for capillaries by the periodic acid Schiff-amylase method (2). The capillary-to-fiber ratio was calculated as the number of capillaries in an area divided by the number of fibers in the same area. Capillaries identified in the borders were counted as one-half.

Statistical analysis. All variables were examined for normality both graphically and statistically. Means and SDs were calculated. An unpaired *t*-test was used to detect differences between those who were tested at T1 but did not participate in T2 and those who returned at T2. Repeated-measures ANOVA was used to test for changes over time. Statistical significance was accepted if the two-tailed *P* value was <0.05. The relationship between the change in strength and the change in CSA was tested by using analysis of covariance. The software package Sigmaplot/SigmaStat (SPSS, 1997) was used for the analysis.

RESULTS

Subject characteristics. The general characteristics of the nine men tested both at T1 and T2 are presented in Table 1. There was no difference at T1 in age, body mass index, and muscle strength between those who did not participate and those who came back for T2.

The reported weekly energy expenditure in sports and recreational activity at T1 and T2 was 834 ± 1,409 and 578 ± 489 kcal, respectively ($n = 5$; $P > 0.05$), and none had continued resistance training after T1. The subjects were taking an average of 0.4 ± 0.7 and 1.8 ± 1.2 ($P < 0.012$) medications at T1 and T2, respectively. The number of self-reported health problems was 2.0 ± 1.1 and 3.2 ± 0.8 ($P < 0.05$) in T1 and T2, respectively.

Strength measurements. Significant losses in muscle strength ranging from 23.7 to 29.8% were noted in the extensors and flexors of the knee at both angular

Table 1. *General characteristics of subjects*

	1985–86	1997–98	Delta	P Value
Age, yr	65.4 ± 4.2	77.6 ± 4.0	12.2 ± 0.5	<0.001
Body weight, kg	76.5 ± 7.3	75.5 ± 9.8	−1.0 ± 3.1	0.367
Height, cm	173.9 ± 5.8	172.7 ± 5.9	−1.2 ± 0.8	0.003
BMI, kg/m²	25.3 ± 1.8	25.3 ± 2.5	−0.02 ± 1.1	0.957

Values are means ± SD for returning subjects ($n = 9$) only. BMI, body mass index. Delta, change between 1985–86 and 1997–98 values.

Table 2. *Longitudinal changes in isokinetic muscle strength in older men after 12 yr*

	n	1985–86	1997–98	Delta	%Change	%Change/yr	P Value
Knee extensors							
60°/s	9	161 ± 37	124 ± 39	-38 ± 24	-23.7 ± 14.6	-1.98 ± 1.22	0.001
240°/s	8	83 ± 23	62 ± 29	-24 ± 18	-29.8 ± 22.9	-2.48 ± 1.91	0.007
Knee flexors							
60°/s	9	102 ± 34	72 ± 31	-30 ± 29	-28.5 ± 23.3	-2.37 ± 1.94	0.015
240°/s	8	63 ± 22	44 ± 27	-19 ± 23	-29.4 ± 35.4	-2.45 ± 2.95	0.03
Elbow extensors							
60°/s	9	40 ± 5	32 ± 8	-7 ± 7	-19.4 ± 18.6	-1.61 ± 1.55	0.01
180°/s	8	26 ± 7	24 ± 9	-3 ± 10	-9.0 ± 36.8	-0.75 ± 3.06	0.43
Elbow flexors							
60°/s	9	39 ± 8	32 ± 7	-7 ± 7	-16.4 ± 18.7	-1.37 ± 1.56	0.022
180°/s	8	31 ± 8	22 ± 6	-9 ± 10	-26.5 ± 30.0	-2.21 ± 2.50	0.027

Values are means $\pm$ SD in N·m for returning subjects only (n).

velocities tested (Table 2). Eight subjects showed a loss in strength of the knee extensors and flexors when tested at 60°/s. At faster speeds, all subjects showed a decrease in muscle strength of the knee extensors (7 of 9 for the flexors). Overall, the rate of loss was 2.0 and 2.5%/yr for the extensors and flexors, respectively.

At 60°/s, the elbow extensors and flexors showed losses of 19.4 and 16.4%, respectively (see Table 2). At 180°/s, the loss in strength of the elbow flexors was 26.5%, and the elbow extensors showed no change. When tested at 60°/s, a reduction in strength of the elbow extensors and flexors was seen in eight and seven subjects, respectively. At faster speeds, five subjects showed a decrease in muscle strength of the elbow extensors and six in the elbow flexors. The rate of loss was ~1.6 and 1.4–2.2%/yr for the extensors and flexors, respectively.

Total work performed by the extensors of the knee during a 25-maximal-contraction test declined from 1,700 to 1,284 J ($P = 0.014$) over 12 yr or 2.3%/yr.

CT. The CSAs of the thigh (all tissues), all muscles, quadriceps femoris muscle, and flexor muscles are presented in Table 3. A significant reduction in all CSAs was observed, with the percent change ranging from 12.5 to 16.1%. Smaller total thigh, all muscle, quadriceps femoris muscle, and flexor muscle areas at T2 were noted in six of seven subjects.

Analysis of covariance showed that muscle strength at T1 ($P < 0.001$) and the change in muscle CSA ($P < 0.05$) over time were independent predictors of strength levels at T2. Together, strength at T1 and the change in muscle CSA account for 90% of the variability in strength at T2. If strength at T1 is held constant, a decrease of 1 cm^2 in CSA was associated with a reduction of 2.68 N·m in strength at T2.

Muscle biopsy. The fiber-type distribution, fiber CSA, and capillary-to-fiber ratio are presented in Table 4. A significant decrease in the percentage of type I fibers was seen, but no changes in the mean fiber area of either fiber type were noted. Capillary density was significantly reduced after 12 yr ($P < 0.05$).

DISCUSSION

To our knowledge, the present study is the first report on longitudinal changes in muscle strength, muscle CSA, and muscle fiber distribution and size in the same cohort of elderly subjects. The main findings of the present study were *1*) a significant reduction in the isokinetic strength of all muscle groups tested at two angular velocities except for the elbow extensors when tested at 180°/s; *2*) a significant decrease in muscle CSA; *3*) a decrease in percentage of type I fibers with no change in type I or II mean fiber area; and *4*) a decrease in the capillary-to-fiber ratio.

Muscle strength. We observed a significant loss of muscle strength with age at both slow and fast angular velocities. Other longitudinal studies of isokinetic strength of the knee extensors in men have shown significant reductions in isokinetic strength. For example, Aniansson et al. (3, 4) studied men 7 ($n = 23$) and 11 yr ($n = 9$) after a first evaluation (initial mean age 69 yr). Isokinetic strength measured at 60°/s had declined by 21 and 35%, respectively, at follow-up. They did not find significant changes in strength at faster velocities (180–300°/s). However, in a different study, Aniansson et al. (5) reported a 27% loss at 180°/s in 75-yr-old men after 5 yr.

Our findings are not in agreement with those of Greig et al. (16), who reported no change in knee-extensor strength in a group of 14 men and women after 8 yr (median follow-up age 81.5 yr). In that study, however, testing was done isometrically, and the subjects were fairly active (3–5 on a 1–6 scale).

Table 3. *Longitudinal changes in midthigh muscle cross-sectional area in older men after 12 yr*

	1985–86	1997–98	Delta	%Change	P Value
Total thigh	192.8 ± 21.1	168.4 ± 19.1	-24 ± 14.7	-12.5 ± 7.2	0.005
All muscles	135.7 ± 18.9	115.8 ± 19.9	-19.8 ± 11.5	-14.7 ± 8.7	0.004
Extensors	64.8 ± 9.5	54.5 ± 10.2	-10.3 ± 5.2	-16.1 ± 8.1	0.002
Flexors	34.2 ± 5.2	29.0 ± 4.0	-5.2 ± 4.2	-14.9 ± 10.1	0.017

Values are means $\pm$ SD in cm^2 for returning subjects ($n = 7$) only.

Table 4. *Longitudinal changes in muscle fiber type and size and capillary density in older men after 12 yr*

	1985–86	1997–98	Delta	%Change	P Value
Type I					
Percentage of all fibers	60 ± 9	40 ± 9	−20 ± 9		0.003
Mean fiber area, μm²	4,190 ± 410	4,190 ± 990	0 ± 900	0 ± 22.2	0.995
Type II					
Percentage of all fibers	40 ± 9	60 ± 9	20 ± 9		0.003
Mean fiber area, μm²	4,150 ± 670	3,980 ± 830	−170 ± 1,040	−2.5 ± 25.3	0.708
Capillary density, capillaries/fiber	1.39 ± 0.21	1.08 ± 0.13	−0.31 ± 0.28	−20.3 ± 20.7	0.043

Values are means ± SD for returning subjects ($n = 6$) only.

The annual decline in strength observed in the present study ranged from 1.4 to 2.5%, depending on the muscle group and the angular velocity. Other longitudinal studies have reported annual decline rates ranging from 1.4 to 5.4% (3–6, 31, 34). In a previous cross-sectional study, which included the subjects participating in the present investigation, the estimated annual decline in strength was 1.5 N·m^{-1}·yr^{-1} (14). From the present data, the calculated loss was 3.2 N·m^{-1}·yr^{-1}, supporting the suggestion that cross-sectional data underestimate true aging losses (6, 9).

The different rates reported by various investigators may reflect differences in study populations, levels of physical activity, muscle groups tested, and testing methodologies, among other factors. We observed larger reductions in isokinetic strength in muscles of the lower extremities compared with the upper extremities. This is similar to the results of a recent cross-sectional study in which leg peak torque (sum of knee extensor and flexor peak torque) declined at a faster rate than arm peak torque (sum of elbow flexors and extensors) (23). Together, these observations suggest that studies of sarcopenia must consider the functional demands placed on individual muscle groups by different activities.

Of the causes of interstudy variation, physical activity is of particular interest because it has been shown to influence muscle strength in the elderly (28, 31). None of the subjects in the present study had continued strength training after T1, and it could be suggested that our data show a decline in energy expenditure. However, because of the small sample size, limited information on habitual physical activity, and the variability in the change, we cannot evaluate appropriately the contribution of physical activity in the present study.

Muscle size. Several factors may contribute to muscle weakness in the elderly, including a quantitative loss of muscle mass and/or a change in the intrinsic properties of muscle fibers. Very few longitudinal studies have evaluated changes in muscle CSA with age. In the present study, the reduction in the CSA of all muscles, quadriceps femoris muscle, and flexors was 14.7, 16.1, and 14.9%, respectively. The magnitude of our findings differ from the 6.4% decrease reported by Greig at el. (16) in quadriceps CSA after 8 yr (mean age 81.5 yr for women and 83 yr for men). These researchers, however, changed the methodology to evaluate CSA in the second evaluation (ultrasound vs. CT scan), and the duration

of the follow-up period was 4 yr shorter. With the use of cross-sectional data from the study of Lexell et al. (22), it can be estimated that, after age 50, the reduction in muscle CSA is ~1%/yr. In the present study, however, the reduction was 1.4%/yr, suggesting that cross-sectional studies may underestimate true aging loss in muscle size.

The reduction in muscle CSA and the strength level at T1 were independent predictors of muscle strength at T2. In other words, baseline strength and changes in muscle size were significant contributors to the loss of strength with aging.

Muscle biopsy findings. Very few studies have evaluated longitudinal changes in muscle fiber-type composition, fiber area, and capillary density with advancing age. Our main findings in six subjects were a significant reduction in the percentage of type I fibers, no change in MFA, and a decrease in capillary density.

With regard to the fiber-type distribution, Aniansson and colleagues (3) reported a significant decrease in percentage of type IIB fibers during the last 4 yr of an 11-yr follow-up study. However, there was no significant change over the 11-yr period. In another longitudinal study, an increase in percentage of type I fibers was noted after 20 yr, but the subjects in that study were runners with a mean age at follow up of 47–50 yr (33).

The reduction in percentage of type I fibers and the corresponding relative increase in percentage of type II fibers observed in the present study are unexpected findings, because reviews of the literature (mainly of cross-sectional studies) suggest that fiber-type distribution does not change with age (27). There may be three possible explanations for our findings. The methodological shortcomings of the muscle biopsy technique suggest that we should interpret our findings with caution. According to Lexell et al. (21), for an ordinary-sized biopsy (~600 fibers) with 50% type I fibers, the 95% confidence interval for the estimate of this proportion is as large as 40–60%. Also, the mean proportion of type I fibers in different areas of vastus lateralis muscle could vary from 32 to 65% (19). Secondly, recent reports show that a very high percentage (range 20–53%) of muscle fibers from older subjects coexpress two or three myosin heavy chain isoforms (see Ref. 1). This suggests that histochemical techniques could misclassify fibers that coexpress slow and fast isoforms. Finally, we should consider the possibility of selection bias, because our subjects were healthy volunteers for an exercise study at T1 with minor health problems at T2 and, therefore,

may not be comparable to other study samples in the literature.

We did not observe changes in MFA of either type, an observation that could suggest that muscle atrophy results from a reduction in the number of muscle fibers. Lexell and colleagues (22) studied whole muscle cross sections of the vastus lateralis obtained during autopsies and reported that age-related muscle atrophy was mainly due to a reduction in the number of muscle fibers and, to a lesser extent, to a reduction in type II, but not type I, fiber size. With regard to the changes in mean fiber area, their results are supported by other cross-sectional studies showing that type I mean fiber area is preserved, whereas type II fibers show atrophy (for review see Ref. 27).

Longitudinal studies that use the biopsy technique in older subjects have reported a 14 and 25% reduction in type IIA and IIB fiber size, respectively, after 7 yr and no change in type I fiber size (4). However, after an additional 4 yr, type I and IIA fibers showed 30% hypertrophy (3). The muscle hypertrophy was interpreted as a compensatory adaptation for the loss of motor units in subjects who maintained their level of physical activity.

Our finding that type I mean MFA did not change is in agreement with the literature (see Ref. 27). The absence of a significant reduction in type II mean fiber area, on the other hand, could be explained by the small number of subjects and the fact that an increase in the size of type II fibers was seen in three subjects. This increase could neutralize the atrophy seen in the other three subjects and result in no change in the group average. Also, variability in MFA has been reported to increase with age (20) and could make detection of significant changes over time more difficult. Finally, it may take many decades for significant atrophy to take place, as illustrated by the 24% reduction in type II mean fiber area reported by Lexell et al. (22) over a period of 62 yr.

The number of capillaries per fiber reported in the present study is in the same range as that reported by Aniansson et al. (4) (1.26 ± 0.06), but they did not observe longitudinal changes in a small sample ($n = 4$) of subjects. A significant decrease in the capillary-to-fiber ratio was seen in the present study. This reduction could be associated with the decline in the prevalence of type I fibers, which are known to have a higher capillary-to-fiber ratio compared with type II fibers. A reduction in capillarization could compromise muscle endurance, as shown by the significant reduction in isokinetic total work seen in the present study. Our observations are consistent with cross-sectional studies reporting a lower capillarization in the lateral gastrocnemius of sedentary older subjects (10). The possible influence of physical activity was underlined recently by Chilibeck et al. (8), who reported no differences in capillary-to-fiber ratio in moderately active older subjects compared with younger moderately active subjects.

Biological variability. Significant variability among subjects characterizes age-related changes (20, 31). We observed such variability in our measurements of muscle strength, CSA, and MFA. For example, the changes in the strength of the knee extensors ranged from no change in one subject to a reduction of 76 N·m in another subject, and the reduction in the CSA of quadriceps femoris muscle ranged from 3 to 17 cm² (5–26%). Finally, the changes in type I fiber area ranged from a 27% increase to a 44% decrease, and corresponding changes in type II fiber area ranged from a 26% increase to a 40% reduction.

In conclusion, the present longitudinal study shows a significant reduction in skeletal muscle isokinetic strength, CSA, percentage of type I fibers, and capillary-to-fiber ratio in older men after 12 yr. Our observations underscore the contribution of a quantitative loss in muscle CSA to muscle weakness in the elderly. Furthermore, the magnitude of the changes in this group of healthy men with few medical problems suggests that stronger exercise recommendations are needed to prevent sarcopenia and the early onset of disability. Because the specific changes that occur in terms of muscle fiber type and size vary broadly among individuals, it may be premature to suggest that sarcopenia exclusively affects type II fibers. In addition, the relevance of these results to older, frail populations is not yet clear. Further longitudinal studies in large population samples should be conducted to elucidate the specific mechanisms responsible for muscle weakness in the elderly.

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