Muscle strength and body composition in adult women with Marfan syndrome


Objective. The purpose of this study was to assess skeletal muscle function and body composition in a group of women with Marfan syndrome compared with matched controls.

Methods. The 21 women who were receiving follow-up for Marfan syndrome at our institution, were free of major cardiovascular disease, and consented to the study performed isokinetic and isometric knee extension and flexion maximal strength tests and had their body composition evaluated using dual-energy X-ray absorptiometry (DEXA). The same assessments were done in 19 matched controls.

Results. A significant decrease in lean leg mass with no change in total soft-tissue leg mass was noted in the patients compared with the controls. Peak torque values for the quadriceps and hamstring muscle groups were decreased in the patients, but only quadriceps strength was significantly reduced after normalization for lean leg mass.

Conclusion. The muscle strength reduction in Marfan patients was not fully explained by a decrease in lean leg mass, suggesting qualitative skeletal-muscle alterations related to abnormal fibrillin expression in muscle connective tissue.

Key words: Skeletal muscle, Marfan syndrome, Isokinetic muscle strength, Body composition.

Introduction

Marfan syndrome is a dominantly inherited connective tissue disorder with cardinal manifestations in the ocular, skeletal and cardiovascular systems associated with involvement of the lungs and integument [1, 2]. Mutations in the fibrillin-1 (FBN1) gene located at 15q21.1 explain most of the cases [3]. This gene encodes FBN1, a widely distributed molecule that is a major component of microfibrils in the extracellular matrix. Microfibrils may be important for elastin deposition to form elastic fibres. Recent findings also suggest that FBN1 may not only be important for structural reasons, but also as a participant in TGFβ-related signalling [3, 4]. The key feature of Marfan syndrome is decreased structural integrity of various tissues, most notably the aortic wall, manifesting as dilation of the ascending aorta [5].

Muscle fatigue is often reported by patients with Marfan syndrome although myopathy is not classically considered a component of Marfan syndrome [1, 2, 4, 6, 7]. In addition to apparent muscle underdevelopment, some patients report myalgia or cramps suggesting skeletal muscle involvement. FBN1 is relatively abundant in the skeletal muscle endomysium and perimysium, suggesting a causal link between muscle symptoms and the FBN1 abnormality [8, 9]. In a family with Marfan syndrome myopathy, muscle weakness was segregated with the FBN1 gene mutation and accompanied with presence of a truncated form of fibrillin in vastus lateralis muscle biopsies [10]. In a study of exercise capacity and skeletal muscle strength in a small group of patients with Marfan syndrome, reductions were noted in aerobic capacity and isokinetic peak torque of knee flexion and extension [11]. However, skeletal muscle mass and isometric strength have not been evaluated in Marfan syndrome.

The purpose of this study was to further investigate skeletal muscle function in patients with Marfan syndrome. We studied a group of 21 women with Marfan syndrome but no major cardiovascular involvement, comparing them with healthy women matched on age, and anthropometric characteristics. After assessing daily physical activity levels and self-reported fatigue, we measured lower-limb muscle strength and fatigue under isokinetic and isometric conditions, and we looked for correlation between the results and lean leg mass determined using dual-energy X-ray absorptiometry (DEXA).

Methods

Study design and characteristics of the study participants

The study was approved by our institutional ethical committee. Written informed consent according to the declaration of Helsinki was obtained from all patients and controls before the study. To reduce variability in skeletal muscle performance, we confined the study to women. We first identified all women aged 18–55 yrs who were receiving follow-up at our Marfan syndrome clinic, met international criteria for Marfan syndrome [2], and resided near our institution. Of the 56 patients thus identified, 30 had a history of aortic surgery, significant aortic or mitral regurgitation, or stroke and were not included in the study. In addition, five women declined to participate. The remaining 21 women were included in the study and performed muscle strength testing. Among them, three women declined to return for evaluation of their body composition. All patients were taking conventional doses of selective-β1 blockers as recommended for patients with Marfan syndrome.

The controls were 19 healthy women recruited among the hospital staff and medical school students. We attempted to match as closely as possible controls to the patients on age and anthropometric measurements. None of the controls were taking medications or had symptoms of cardiovascular disease. Body composition was evaluated in only 13 of the 19 controls.

Assessment of the daily level of physical activity

The International Physical Activity Questionnaire (IPAQ) [12, 13] based on self-reported information was administered during face-to-face interviews to assess physical activity across a set of domains including leisure time, domestic and gardening activities, work and transportation. The items are structured to provide separate scores for walking, (W), moderate-intensity (MI) activity and vigorous-intensity (VI) activity, as well as a combined...
score \((W + MI + VI)\) reflecting the overall level of activity. Moderate-intensity activities are those associated with moderate increases in heart and respiratory rates, whereas vigorous-intensity activities are defined as producing major increases in the same variables. Only physical activities performed for at least 10 min at a time are considered. For each item, the frequency (days per week) and duration (time per day) were collected. The volume of activity was computed by weighting each item by its energy expenditure in Metabolic Equivalents of Task (METS) as multiples of the resting metabolic rate. The MET-score was multiplied by the duration of the activity in minutes per week (MET-minutes).

Self-reported fatigue
The self-reported nine-item Fatigue Severity Scale was used [14]. For each item, there is a seven-point response format in which 1 indicates strong disagreement and 7 strong agreement with the statement in the item. The global score is computed as the mean of item scores. Higher scores indicate greater fatigue.

Peak force testing
Maximal isometric and isokinetic strength was measured at peak torque for knee extension and knee flexion of the right leg, using an isokinetic dynamometer (Biodex Medical Systems Inc., Shirley, NY, USA). All measurements were performed by the same experienced investigator (GP). The study participant sat on a chair, which maintained the hips at 90% flexion. The right thigh, pelvis and shoulders were immobilized by straps. The subject was instructed not to hold the lap belt. The rotational axis of the dynamometer lever arm was positioned at the level of the lateral femoral condyle, and the lower leg just above the lateral malleolus was strapped to the lever arm. Automatic compensation for gravitational errors in the vertical plane was achieved by measuring the static moment of the limb-lever system falling passively from the horizontal position. The flexion-extension range was limited to 80° to ensure that all study participants would be able to perform the full movement. During all tests, study participants were instructed to push or pull as fast and as hard as possible. They received vigorous verbal encouragement during the task.

Isokinetic strength measurements. Concentric quadriceps and eccentric hamstring muscle strengths were measured as the maximal force moment (peak torque) during isokinetic knee extension and flexion movements. Strength measurements were preceded by a preconditioning procedure consisting of three series of 20 knee extension and flexion movements at a concentric angular velocity of 180°/s.

Maximal peak torque of the quadriceps was computed first at 120°/s (20 repetitions) then at 60°/s (five repetitions). Next, maximal peak torque of the hamstring muscles was computed from five repetitions at 60°/s then five repetitions at 120°/s. The resting period between measurement sets was at least 2 min. Each measurement set was preceded by a familiarization period. Maximal isokinetic peak torque was defined as the highest value at each velocity.

Isometric strength testing. Maximal isometric strength was measured after isokinetic strength. Three 5-s maximal voluntary isometric contractions of the knee extensors with the knee flexed at 90° were followed by three 5-s maximal voluntary isometric contractions of the knee flexors with the knee flexed at 60°. Full knee extension was the 0° reference point. Contractions were separated by at least 2 min of rest.

Muscle fatigue measurements. Muscle fatigue of the knee extensors was calculated from the 20 maximal repetitions at 120°/s as the percent strength decrease \((\Delta\text{Peak Torque})\) between mean peak torques developed during the first five movements \((R_{1–5})\) and the last five movements \((R_{15–20})\).

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\Delta\text{Peak Torque} = \frac{R_{1–5} - R_{15–20}}{R_{1–5}} \times 100
\]

Body composition evaluation
Body composition was measured using DEXA (Hologic, QDE 1000 W, Hologic Inc.). Lean body mass \((\text{LBMI})\) is the sum of all chemically fat-free soft tissues in the body, excluding bone mineral content. Fat body mass \((\text{FBM})\) is the total amount of fat in soft tissue. Lean leg mass \((\text{LLM})\) and fat leg mass \((\text{FLM})\) of the right leg were derived from total-body scans. Typical precision for total-body scans is 0.75% (total region coefficient of variation with a bone mineral density of 1.0 g/cm²).

Statistical analyses
Statistical tests were run using Statview software (version 5.0, SAS Institute Inc., Cary, NC, USA). Results are reported as means ± s.d. For strength evaluations, two-way ANOVA was used to test for differences between groups, differences between speeds and group-by-speed interaction. Body composition variables in the two groups were compared using the Mann–Whitney U-test. Differences between groups were considered significant when \(P < 0.05\). Spearman’s rank coefficient served to evaluate correlations.

Results
Physical characteristics of the study participants
Age, weight and body mass index were similar in patients and controls (Table 1). Height was slightly but significantly higher in the patients than in the controls \((P < 0.05)\). In each group, physical characteristics were not significantly different between the subgroup of individuals who underwent body composition measurements and the overall study group (Table 2).

Daily activity level
The daily activity level varied widely among patients and among controls. The only significant difference between the two groups was a lower level of vigorous-intensity activity in the patients compared with the controls \((P < 0.05, \text{Fig. 1})\).

| Table 1. Physical characteristics of the patients with Marfan syndrome and the controls |
|---------------------------------|-----------------|-----------------|
| **Controls** & **(n = 19)** & **Marfan** & **(n = 21)** |
| Age (yrs) & 29.5 ± 8.3 (21.1–46.3) & 34.5 ± 8.6 (20.9–53.7) |
| Weight (kg) & 59.1 ± 4.1 (53–68) & 61.7 ± 11.7 (40–82) |
| Height (m) & 1.73 ± 0.04 (1.63–1.83) & 1.75 ± 0.04 (1.65–1.83) |
| BMI (kg/m²) & 19.8 ± 1.24 (18.2–22.7) & 20.0 ± 3.7 (12.6–26.1) |

The values are means ± s.d. (range). \(n\) indicates number of study participants. BMI, body mass index (weight in kg divided by the square of height in m²).

| Table 2. Physical characteristics of the patients and controls who underwent body composition evaluation |
|---------------------------------|-----------------|-----------------|
| **Controls** & **(n = 13)** & **Marfan** & **(n = 18)** |
| Age (yrs) & 31.7 ± 9.0 & 36.2 ± 7.9 |
| Weight (kg) & 58.7 ± 4.1 & 60.7 ± 12.4 |
| Height (m) & 1.72 ± 0.04 & 1.76 ± 0.04 |
| BMI (kg/m²) & 19.8 ± 1.1 & 19.9 ± 3.8 |

The values are means ± s.d. \(n\) indicates number of study participants. BMI, body mass index (weight in kg divided by the square of height in m²).
Self-reported fatigue

The mean Fatigue Severity Scale score was significantly higher in the Marfan patients (5.11 ± 1.18; range 3.3–6.9) than in the controls (3.31 ± 1.08; range 1.9–5.3) (P < 0.05).

Body composition evaluation

LBM and LLM were slightly but significantly lower in the patients than in the controls (P < 0.05, Table 3). Neither variable was related to the levels of vigorous-intensity activity or total activity in the patients or controls. Total soft-tissue leg mass (FLM+LLM) did not differ between the patients (10.3 ± 2.3 kg) and the controls (10.6 ± 0.9 kg).

Muscle performance

Peak torque. Quadriceps peak torque was dependent on speed in both groups (P < 0.001) and was approximately 20% lower in the patients than in the controls (P < 0.01), with no group-by-speed interaction (Fig. 2). This difference between patients and controls was smaller when peak torque was normalized for LLM (peak torque/lean leg mass) in the subgroups whose body composition was evaluated, although the difference remained statistically significant (P < 0.05, Fig. 3). In both groups, the maximal isokinetic peak torque of the quadriceps muscle was positively and significantly correlated with LLM at 60°/s (P < 0.05, Fig. 4), whereas isometric quadriceps strength was correlated with LLM in the patients but not in the controls. Absolute quadriceps peak torque at 120°/s (r = −0.44, P < 0.01) and 60°/s (r = −0.41, P < 0.05) showed weak negative correlations with the Fatigue Severity Scale score.

Hamstring peak torque was also dependent on speed in both groups (P < 0.001) and was approximately 10% lower in the patient group (P < 0.05) at both speeds (Fig. 2). Hamstring isokinetic and isometric peak torque values were slightly but significantly correlated to LLM in the patients but not in the controls. Hamstring peak torque normalized for LLM was not significantly different between the two groups (Fig. 3). Absolute hamstring peak torque was not significantly correlated with the Fatigue Severity Scale score.

Objective muscle fatigue. Quadriceps peak torque decreased significantly over the 20 successive concentric repetitions in both groups, indicating muscle fatigue. The decrease varied widely and was not significantly different between the patient and control groups [median (5th to 95th percentile), −15.2% (−30.8–11.2%) in the patients and −16.2% (−25.7–7.1%) in the controls).

Discussion

The present study documents a decrease in skeletal muscle strength in a group of adult women with Marfan syndrome compared with healthy control women. This decrease was found in both of the investigated muscle groups (quadriceps and hamstring muscles) and under two different measurement
conditions (isometric and isokinetic contraction). In addition, LBM and LLM were decreased in the patients.

Whereas the cardiovascular, ocular and skeletal system abnormalities in patients with Marfan syndrome have been well characterized, little is known about skeletal-muscle structure and function in this disorder. There have been anecdotal reports of histologically documented myopathy in patients with Marfan syndrome or related disorders such as limb girdle muscular dystrophy [7, 15], Duchenne muscular dystrophy [16], ocular myopathy [17], centronuclear myopathy [18] and multicore disease [19].

To our knowledge, a single study investigated muscle performance in patients with Marfan syndrome [11]. Isokinetic muscle strength measurements in 13 patients showed a decrease in knee-flexion concentric peak torque at high velocity [11]. Despite the differences in measurement conditions (isometric vs. isokinetic contraction, flexion in eccentric vs. concentric condition and velocity levels), these data are consistent with our evidence of muscle weakness in Marfan syndrome. However, in this previous study [11], peak torque of the extensor muscles was not significantly different between patients and healthy controls when tested at 60°/s and 240°/s, and maximal isometric strength was not evaluated. In our study, the muscle strength decrease was significant for both isometric and isokinetic knee-extensor contraction.

Muscle strength may decrease as a result of either muscle tissue loss or abnormal muscle contraction. In healthy adults, muscle strength correlates with muscle mass or muscle cross-sectional area [20, 21]. In our study, body composition as evaluated using DEXA was significantly altered in patients with Marfan syndrome compared with healthy controls matched on age and body mass. Although total soft-tissue leg mass was similar in the two groups, LLM was significantly decreased and FLM significantly increased in the patients. Since lean mass is chiefly composed of skeletal muscle, the LLM decrease in the patients indicates a reduction in muscle mass, which may partly explain the decrease in muscle strength. Thus, in the patients, quadriceps and hamstring muscle strength under both isokinetic and isometric conditions correlated significantly with LLM. Moreover, normalizing muscle strength for LLM diminished the difference between patients and controls for the quadriceps and abolished it for the hamstring muscles.

The level of daily physical activity may contribute to determine the total skeletal muscle mass [22, 23]. We cannot rule out that the decrease in lean mass found in our patients was related, at least in part, to a lower level of daily physical activity. The IPAQ scores

FIG. 3. Ratio of peak torque over lean leg mass for the quadriceps and hamstring muscles measured at 120°/s, 60°/s and 0°/s in patients with Marfan syndrome and in controls. Results are reported as means ± s.d. The relative peak torque of the quadriceps differed significantly between the patients and the controls ($P < 0.05$), with no group-by-speed interaction (two-way ANOVA).

FIG. 4. Relation between lean leg mass and maximal peak torque of the quadriceps under isokinetic (120°/s and 60°/s) and isometric (0°/s) conditions in the patients with Marfan syndrome and the controls.
showed that physical activity varied widely both across the patients and across the controls. We found a trend toward less physical activity in the patient group, with a significant difference for vigorous-intensity activity. These results reflect the recommendations made for Marfan patients regarding everyday activities. Moreover, we selected patients who were free of cardiovascular complications such as major aortic dilation or valvular dysfunction and who were therefore free of activity-limiting symptoms. Such patients are informed that sports such as walking, swimming and biking are beneficial when practised at aerobic levels but that vigorous activities such as weight lifting or climbing steep inclines should be avoided. However, we found no relationship linking the level of vigorous-intensity activity or total activity to LLM or muscle strength in either group of individuals, none of whom engaged in strenuous sports. These findings do not support the hypothesis that the lower lean mass in the patients was chiefly related to a lower level of physical activity.

In our study, the decrease in quadriceps muscle strength was larger than the reduction in LLM, as demonstrated by the reduction in the ratio of peak torque over LLM. Thus, qualitative alterations in skeletal muscle tissue may contribute to the muscle weakness in patients with Marfan syndrome. A reduction in elastic fibre content has been reported in joint tissues of patients with Marfan syndrome and may contribute to joint laxity [24]. Conceivably, a reduction in the elastic-fibre component of muscle may alter muscle function. A recent study documenting fibrillin abnormalities suggests that connective-tissue abnormalities within skeletal muscle may play a greater role than muscle-fibre alterations [10]. Fibrillin is normally abundant in the endomysium and perimysium of skeletal muscles. Thus, muscle function abnormalities in Marfan syndrome may be related to poor anchoring of the muscle-fibre basement membrane to the extra-cellular matrix. Skeletal muscle function may also be affected by overactivation of TGF-β signalling pathway which has been reported to be associated with FBN1 abnormality [3, 4, 25].

All our patients with Marfan syndrome were taking selective β1-blocking drugs to prevent aortic disease [26]. None of the controls was taking such drugs. Alterations in both endothelium-dependent dilation and maximum dilator reserve capacity have been reported in patients with Marfan syndrome [27, 28]. However, it is unlikely that impaired skeletal muscle blood flow caused the reduction in maximal muscle strength documented in our patients, since the study exercise was of brief duration and confined to a small number of muscle groups. Expected increases in total-body O₂ consumption and cardiac output are small with such exercise protocols, and no significant heart-rate changes occurred during exercise in the patients or controls (data not shown). Moreover, previous studies of the effect of β1-blockers on muscle function do not support a role for β1-blocker therapy in the muscle-strength decrease seen in our patients. Thus, maximal isokinetic torque and maximal dynamic muscle power measured as the highest 5 s power output during a 30 s maximal exercise test were not affected by β1-selective blockade [29]. Similarly, the maximal dynamic muscle strength decline seen during isokinetic endurance testing of the knee flexor or extensor muscles was not influenced by atenolol treatment [29].

Fatigability is a major complaint of patients with Marfan syndrome [6]. Fatigue Severity Scale scores in our study indicated greater fatigue in the patients than in controls matched on age, gender and anthropometrics. Interestingly, despite reports of greater fatigue in the Marfan patients, there was no evidence of a difference in objective muscle fatigue between the two groups. In both groups, the decrease in quadriceps muscle strength during an isokinetic exercise at 120°/s varied widely across individuals, but no statistically significant or clinically relevant difference was noted between the patients and controls. Although one would not expect β-blockers to affect maximum voluntary isometric contraction of the quadriceps, we cannot exclude that frequent complaints of subjective fatigue might reflect a limitation in aerobic capacity induced by β-blocker treatment, likely through limitation in the cardiac output increase. However, it should also be noted that in the absence of β-blocker treatment a 30% decrease in peak oxygen uptake has been found in women with Marfan syndrome compared to normal age-matched untrained individuals [11], although peak heart rate and systolic blood pressure were comparable to predicted values.

Our study has several limitations. We did not record EMG activity to rule out involvement of the peripheral nervous system. Muscle strength and proprioception are physiologically related in the control of limb movements. Although we did not assess sense of joint position, none of our Marfan patients had difficulty of gait control or ataxia suggesting some abnormality of proprioception. Muscle biopsy would be needed to further investigate the muscle alterations. In one patient with predominantly proximal muscle wasting, electromyography showed polyphasic action potentials and histology disclosed atrophy of Type II muscle fibres [30].

In conclusion, we documented a reduction in the maximal strength of the quadriceps and hamstring muscles in women with Marfan syndrome. This strength reduction was not fully explained by a reduction in LLM, suggesting a role for qualitative muscle alterations related to fibrillin abnormalities in the connective tissue of skeletal muscle. Further investigations are needed to characterize the skeletal muscle changes in Marfan syndrome.

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The authors have declared no conflicts of interest.

Rheumatology key messages

- Quadriceps muscle strength measured in isometric and isokinetic conditions is decreased in women with Marfan syndrome.
- Decrease in lean leg mass only partly explains this decrease.

References


