Relationship of skeletal muscle mass, muscle strength and bone mineral density in adults with cystic fibrosis

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ABSTRACT

Few studies have investigated peripheral muscle strength and quality in patients with cystic fibrosis (CF). The present study tested the isometric and isokinetic strength of the quadriceps and hamstrings using an isokinetic dynamometer and a strength-testing chair in 25 CF adults and 25 controls. Total body and leg muscle mass were determined by dual-energy X-ray absorptiometry, and bone mineral density (BMD) was also measured. Both muscle strength and muscle mass (total body and leg) were decreased in the CF group. In both groups there was a highly significant relationship between quadriceps strength and leg muscle mass (CF, $r = 0.7$, $P < 0.0002$; controls, $r = 0.6$, $P = 0.0013$). When strength was normalized for muscle size, there was no significant difference between the two groups. Total body and leg BMD were significantly reduced in CF subjects compared with controls. However, when corrected for height, the differences disappeared. There was a significant relationship found between leg muscle mass and leg BMD. We conclude that CF adults are significantly weaker than controls. This is due to lower muscle mass, and not to a reduced force-generating capacity of the muscle, implying that there is no decrease in the quality of CF muscle. BMD is also reduced in CF subjects, and this appears to be related to shorter stature in this group.

INTRODUCTION

Cystic fibrosis (CF) is the most common lethal genetic disorder occurring in Caucasians. Due to improved care and a better understanding of the disease, life expectancy has risen to 31 years of age, and is continuing to rise. In the U.K. alone, adult numbers are increasing by 150 per year [1]. With this increased longevity, it is important to maintain quality of life and functional activity. Over the last decade there have been increasing reports of low bone mineral density (BMD) in CF patients [2,3], especially in end-stage disease, and fractures involving trabecular sites such as the ribs and spine have been reported to be more prevalent in CF adults than in the general population [4]. However, little attention has been paid to other areas of the musculoskeletal system, such as muscle strength and function. Risk factors for osteopenia in this group of patients include malnutrition, gonadal dysfunction, reduced physical activity and glucocorticoid therapy, all of which can also affect muscle strength.

Studies to date include that of Mier et al. [5], who, although primarily investigating respiratory muscle strength, also found quadriceps strength to be reduced in CF patients to 68% of control values, although no mention of statistical significance was given. Lands et al. [6], while investigating the relationship of respiratory muscle strength to peripheral skeletal muscle strength, mentioned the latter to be reduced in CF subjects when

Key words: bone mineral density, cystic fibrosis, muscle mass, skeletal muscle strength.

Abbreviations: BMD, bone mineral density; CF, cystic fibrosis.

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assessed by cycle ergometry. The decrease appeared to be due to a lower lean body mass, as determined from skinfold thicknesses. The techniques used to measure muscle strength, muscle size and body composition have, in the past, been rather crude, and a question mark still remains over whether the quality of CF muscle is impaired. The present study uses newer validated techniques for measurement of the above parameters [7], and aims to determine the relationship between (i) muscle mass and strength, (ii) muscle and bone mass in adults with CF as compared with healthy age-sex-matched controls, and (iii) the quality of CF muscle.

METHODS

Study subjects
A total of 50 subjects participated in the study between November 1997 and March 1998; these comprised 25 stable patients with CF (20 males and five females) and 25 age- and sex-matched healthy controls. The control group consisted of sedentary staff and friends who had limited knowledge of the techniques used. They were not taking any medication that could affect muscle or bone. The patients were recruited from either outpatient clinics or hospital wards. The diagnosis of CF had been made previously by sweat tests and genotyping, together with the appropriate clinical manifestations. All patients were taking vitamin A and vitamin D supplementation, and were clinically stable. The characteristics of the subjects studied are presented in Table 1. The control and CF groups did not differ with respect to age. The CF group was shorter and weighed less than the controls. The lung function of the CF group was variable, with values for % predicted forced expiratory volume in 1 s of between 20 and 101%. Spirometry was not carried out on the controls; they were presumed normal, and were excluded from the study if any history of lung pathology was present.

The local ethics committee approved the study, and signed informed consent was obtained from all participants, in accordance with the Declaration of Helsinki (1989).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CF (n = 25)</th>
<th>Control (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28 (8)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.0 (9.1)</td>
<td>177.2 (8.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.6 (9.4)</td>
<td>77.5 (12.6)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.9 (2.2)</td>
<td>24.6 (2.9)</td>
</tr>
<tr>
<td>FEV₁ predicted (%)</td>
<td>20–101</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 1: Details of CF patients and control subjects

FEV₁, predicted (%), % predicted forced expiratory volume in 1 s. Values are means (S.D.). Significance of differences: * P < 0.05.

Determination of muscle strength
The maximum isometric strength of the quadriceps was measured as the best of three contractions using a strength-testing chair [8] (coefficient of variation < 10%). While sitting comfortably with the hip and knee joints at 90°, subjects were asked to push as hard as possible against a strain gauge positioned just above the ankle. A seatbelt tightened securely over the lap prevented hip extension. The input from the strain gauge was amplified and recorded on light-sensitive paper. Maximum activation was verified by the twitch superimposition test [9].

The isometric strength of the quadriceps and hamstrings was also determined using an isokinetic dynamometer (KinCom; Chattec Corp., Chattanooga, TN, U.S.A.). This is a hydraulically driven, microcomputer-controlled device for the testing, measurement and rehabilitation of human joint function [10]. The subject performs a movement against a resistance provided by the machine, via a rotating lever arm system. The seating position was again with hip and knee joints at 90°, with a seat belt over the shoulder as well as the lap. Measurements of isokinetic concentric contractions were also obtained from the KinCom at two different speeds, 60° and 200°/s. The maximum of three attempts was recorded. All tests were carried out on both legs, and the average value calculated (coefficient of variation < 10%). All measurements had gravity compensation applied.

Handgrip strength was measured using a Jamar hand dynamometer, with the arm by the subject’s side and the elbow extended. The subject was asked to squeeze the handles together with as much force as possible. The best of three attempts was recorded (coefficient of variation < 10%).

Muscle contractile properties
The rates of relaxation and contraction of the quadriceps muscles were measured using the percutaneous stimulation technique (coefficient of variation 10%). Two rubber electrodes were placed over each end of the muscle, and stimulation was generated using square wave pulses. The current at 1 Hz was increased to as high as the patient could tolerate. The subjects were asked to relax the muscle, and three twitches were recorded. The rate of contraction was measured as the time from the onset of stimulation to peak force. The rate of relaxation was measured as the time from peak force to half-peak force.

Cross-sectional area and muscle mass
The cross-sectional area of the thigh muscles and of the bone of the right leg was measured in all subjects by anthropometric estimates of limb circumference and anterior and posterior skinfolds at half femur height.
BMD and regional tissue composition
Values for total-body and leg BMD were gained from DEXA scans (DPX-L; Lunar Radiation Corp., Madison, WI, U.S.A.). The machine was calibrated daily and had a precision error of < 0.01 g/cm². The bone densities are expressed as a percentage of that of age- and weight-matched controls taken from the large Lunar database.

Advanced analysis of the scans involved dividing the body up into specific regions and calculating BMD, lean mass and fat mass. This enabled muscle mass in each leg to be measured, and therefore the force per unit mass to be calculated (coefficient of variation 1–2%).

Analysis
SPSS Version 8.0 for Windows software was used. Within each group there was no significant difference between right and left legs, and therefore data are presented for the average of the two legs. Comparisons between the patients and controls were made using Student’s unpaired t tests. Comparisons between values measured in the same group were made using the Pearson correlation. Relationships between strength and lean body weight, and between lean body mass and BMD, were analysed by linear regression analysis. Bone mass values (g/cm²) were adjusted for height and weight using analysis of covariance. A P value of < 0.05 was considered significant. Throughout this paper results are quoted as mean (S.D.), apart from in Figures, where bars denote S.E.M.

RESULTS

Muscle strength
The isometric quadriceps strength of the CF group was 66% of that of the controls (Table 2) when tested in the strength testing chair and the KinCom (P < 0.0001). It should be noted that the values for isometric strength from the two devices are different because of variations in the lever systems. The isokinetic (dynamic) contractions (Figure 1A) of the quadriceps were also weaker in the CF group at both measurement speeds (P < 0.001). Measurements in the CF group showed decreases in strength of 32% at 60°/s and 36% at 200°/s. No inhibition was found within the quadriceps muscles using the twitch superimposition test in any subject. This proved that the muscles were performing maximum voluntary contractions.

Isometric and dynamic hamstring strengths were also significantly lower in the CF group. Isometric strength was 75.6% that of controls and isokinetic strength was 71.8% that of controls (Figure 1B). Two CF subjects suffered from right knee pain and did not undergo right leg testing on the KinCom.

Handgrip strength in the CF group was 81.5% that of controls (P = 0.04). Two of the CF group underwent testing of one arm only.

Contractile properties
No differences were found in the rate of contraction (P = 0.93) or the rate of relaxation (P = 0.34) between the two groups (Figure 2). Three CF subjects and one control subject could only tolerate the electrical stimulation of one leg.

Table 2  Strength of right and left quadriceps, hamstrings and handgrip in 25 adults with CF and 25 controls

<table>
<thead>
<tr>
<th>Muscle strength</th>
<th>CF</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isometric quadriceps; chair (N)</td>
<td>303.2 (113.9)</td>
<td>461.2 (117.6)**</td>
</tr>
<tr>
<td>Isometric quadriceps; KinCom (N)</td>
<td>423.8 (135.8)</td>
<td>638.3 (167.3)**</td>
</tr>
<tr>
<td>Isokinetic quadriceps; KinCom 60°/s (N)</td>
<td>363.5 (95.7)</td>
<td>530 (118.2)**</td>
</tr>
<tr>
<td>Isokinetic quadriceps; KinCom 200°/s (N)</td>
<td>272.2 (78.8)</td>
<td>428.1 (118.2)**</td>
</tr>
<tr>
<td>Isometric hamstrings; KinCom (N)</td>
<td>170.1 (49.7)</td>
<td>234.4 (75.1)*</td>
</tr>
<tr>
<td>Isokinetic hamstrings; KinCom 60°/s (N)</td>
<td>234.4 (58.6)</td>
<td>325.1 (93.9)**</td>
</tr>
<tr>
<td>Isokinetic hamstrings; KinCom 200°/s (N)</td>
<td>243.5 (58.1)</td>
<td>340.7 (91.4)**</td>
</tr>
<tr>
<td>Handgrip (kg)</td>
<td>38 (10.3)</td>
<td>46.6 (9.9)*</td>
</tr>
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Figure 1  Muscle strength evaluated by the isokinetic dynamometer in (A) the quadriceps and (B) the hamstrings. Isokinetic contractions were carried out at speeds of 60°/s and 200°/s.
Figure 2 Average rates of quadriceps contraction and relaxation in CF and control groups

Table 3 Cross-sectional area (CSA) and muscle mass

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA (cm²)</td>
<td>71.7 (19.2)**</td>
<td>102.4 (25.2)</td>
</tr>
<tr>
<td>Total body muscle mass (g)</td>
<td>47.346 (7.695)*</td>
<td>56.735 (9.199)</td>
</tr>
<tr>
<td>Leg muscle mass (g)</td>
<td>7.627 (1.409)**</td>
<td>10.567 (1.897)</td>
</tr>
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</table>

Table 4 BMD data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-body BMD (g/cm²)</td>
<td>1.17 (0.13)</td>
<td>1.27 (0.11)*</td>
</tr>
<tr>
<td>Total leg BMD (g/cm²)</td>
<td>1.22 (0.14)</td>
<td>1.40 (0.14)**</td>
</tr>
<tr>
<td>Total-body Z score</td>
<td>-0.04 (range 1.44 to -2.67)</td>
<td>0.7 (range 3.09 to 1.22)</td>
</tr>
<tr>
<td>Total-body Z scores &lt; -1 (%)</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

BMD and leg muscle mass

The total-body BMD of the CF group was 92.1% that of the controls (Table 4). Analysis of covariance, allowing for (1) height and (2) height plus weight, found no significant differences between subjects and controls. The mean total leg BMD was also less in the CF group (87.7% of control value); again, analysis of covariance, allowing for lean mass, found no difference between subjects and controls.

There was a significant relationship between total leg muscle mass and leg BMD in both groups (CF, $r = 0.73$, $P < 0.0001$; controls, $r = 0.68$, $P = 0.0002$). There was also a correlation between quadriceps strength and total leg BMD (CF, $r = 0.5$, $P < 0.01$; controls, $r = 0.6$, $P = 0.001$).

DISCUSSION

The results from the present study clearly demonstrate that adult patients with CF have significantly lower peripheral muscle mass and strength when compared with matched control subjects. This is the first time that extensive muscle testing, using both static and dynamic tests, has been carried out in such a group. We have demonstrated that there is a strong correlation between leg strength and lean body mass, which confirms the limited findings of Lands et al. [6]. The present study also shows that individual leg muscle mass, when measured by DEXA, is highly correlated to leg strength, with the relationship being the same for CF patients and controls. Handgrip strength, as a measure of upper limb strength, showed less of a decrease compared with the lower limbs. This is in keeping with decreased levels of physical activity being a cause of lower limb muscle weakness in subjects with CF. Leg muscle mass was also proportionally lower than total body muscle mass in CF subjects, which again might be explained by the relative lack of activity of the lower limbs.

There has been much debate about the quality of muscle in subjects with CF, and whether the disease process affects it. Boas et al. [11] reported that male...
adolescents with CF had lower anaerobic performance than healthy controls, and that power per lean body mass was less than in controls. It should be noted that adolescents are not an ideal group from which to draw conclusions, as their muscle is still developing and maturational factors will play a large role. In contrast, we could find no evidence of abnormal muscle quality in our 25 adult patients. The speeds of contraction and relaxation (contractile properties) were normal, the decrement in dynamic strength was similar at different speeds, and the force-generating capacity (strength per unit of muscle) was the same in the CF subjects and the controls. These are important findings, and indicate that the difference in strength production must be due to the difference in the volume of muscle. Associated skeletal muscle atrophy does occur with gross malnutrition and severe ill health [12], both of which can occur in CF. Indeed, Szeinberg et al. [13] found changes consistent with selective atrophy of type II (fast-twitch) muscle fibres in malnourished male CF patients, and other studies suggest that the muscle oxidative enzymes are impaired [14]. However, we could find no evidence of type II fibre loss in adults with varying disease severity (mean % predicted forced expiratory volume in 1 s = 52%), as the contractile properties appeared to be unaffected. It seems, therefore, that CF disease itself does not change muscle quality, but that the associated poor nutritional status might do so. Muscle biopsies would be needed for a definitive answer.

Numerous studies have documented the occurrence of low BMD in children [15,16] and adults [3,4] with CF. Many factors could be contributing to this, including vitamin D deficiency, hypogonadism, low body weight and decreased physical activity, all of which can also lead to decreased muscle strength. The BMD in our adults, although reduced for both total body and leg, was not significantly different from that of controls when corrected for (1) height and (2) height plus weight. Since adjustment for height alone abolished the difference between subjects and controls, this suggests that smaller bone size in the CF group explains the lower total-body and leg BMD. It should be noted that total-body BMD measurements may be more representative of cortical bone. Other studies have found reduced regional BMD in CF patients to be due to a combination of decreased volumetric BMD and reduced bone size, rather than reduced bone size alone [2,3].

We hypothesized that a decrease in muscle mass would be associated with a decrease in the BMD of the anatomically related bone, and there was indeed a strong correlation between leg muscle mass and leg BMD. This is most probably due to the fact that factors controlling muscle and bone losses are similar. Reduced muscle pull on bone could also play a part in any reduction in BMD. These findings have implications for clinical practice. Firstly, they confirm the importance of body mass index in these patients. Good nutrition and maintenance of body mass index should help patients with CF to gain and maintain muscle mass, muscle strength and BMD. There is increasing recognition that muscle mass and strength are important for bone health, and that increasing muscle strength through an increase in muscle mass may have positive effects on BMD. Weight-bearing activity is important for bone acquisition in children and adolescents, and has also been shown to slow down bone loss in postmenopausal women [17]. The CF population tends to do less physical activity due to decreased aerobic capability. Strength training programmes should be encouraged, and should be devised for individual patients according to ability, as this could help to increase individual muscle strength and maintain site-specific BMD in the future, along with an improvement in quality of life.

In summary, adults with CF, when compared with controls, are significantly weaker; this is due to a lower muscle mass and not to reduced force-generating capacity of the muscle. This means that the CF muscle should have the ability to generate strength if the volume of muscle is increased. There was a strong correlation between leg muscle mass and leg BMD, and this is probably due to the fact that factors controlling both muscle mass and bone mass are similar.

REFERENCES


Received 19 January 2000/15 May 2000; accepted 14 June 2000