Strength training and albuterol in facioscapulohumeral muscular dystrophy

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Abstract—*Background:* In animals and healthy volunteers β2-adrenergic agonists increase muscle strength and mass, in particular when combined with strength training. In patients with facioscapulohumeral muscular dystrophy (FSHD) albuterol may exert anabolic effects. The authors evaluated the effect of strength training and albuterol on muscle strength and volume in FSHD. *Methods:* Sixty-five patients were randomized to strength training of elbow flexors and ankle dorsiflexors or non-training. After 26 weeks albuterol (sustained-release, 8 mg BID) was added in a randomized, double-blind, placebo-controlled design. Primary outcome was maximum voluntary isometric strength (MVIC) at 52 weeks. Secondary outcomes comprised dynamic strength and muscle volume. *Results:* Training and albuterol were well tolerated. Training of elbow flexors did not result in a significant effect on MVIC, but dynamic strength improved significantly. Elbow flexor MVIC strength increased significantly in albuterol vs placebo treated patients. Ankle dorsiflexor strength decreased in all groups. Eleven out of twelve non-trained muscles in the albuterol group showed a positive effect on MVIC compared to the placebo group ($p < 0.05$ in seven muscle groups). Muscle volume decreased in the placebo-treated, and increased in the albuterol-treated patients. No synergistic or antagonistic effects were observed between training and albuterol. *Conclusions:* In FSHD strength training and albuterol appear safe interventions with limited positive effect on muscle strength and volume. Consequences of prolonged use are presently unclear, which precludes routine prescription.

NEUROLOGY 2004;63:702–708

With its estimated prevalence of 1 per 20,000, facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy after Duchenne dystrophy and myotonic dystrophy.[1] Although its association with a reduction in number of D4Z4 repeat units at 4q35 was recognized in 1991,[2,3] the pathogenic mechanisms relating this deletion to the phenotype are unclear. The decline in muscle strength and mass is progressive over years and follows a general pattern of clinically affected muscles, but there is a large, unexplained, interindividual variability in rate of progression, even within those sharing the same mutation.[1] The variable course within families and the typical asymmetric weakness led to the hypothesis that daily exertion might be responsible for disease progression.[4,5] Four published studies on the effects of strength training in neuromuscular disorders included as few as 13 FSHD patients.[6-9] Data on muscle strength in these FSHD patients suggest a positive effect of strength training and do not point toward susceptibility to muscle injury. However, limitations in design of these studies preclude firm conclusions. The benefit of strength training in FSHD patients is not defined.

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In animals and healthy volunteers β2-adrenergic agonists, such as clenbuterol and albuterol, increase muscle strength and muscle mass through their influence on muscle protein metabolism and contractile activity.[10] In a pilot study and a subsequent randomized, controlled trial in FSHD patients albuterol induced a moderate gain in isometric muscle strength and lean body mass when used for 12 to 26 weeks.[11,12] After 52 weeks of medication lean body mass was still increased, but patients failed to retain the gain in strength. These findings suggest an anabolic effect that wears off with prolonged use. The strength-increasing effect of β2-adrenergic agonists might be augmented when the β2-sympathicomimetic is administered in combination with resistance exercise.[13-16]

Because we expected an additive effect of training on the effect of the β2-adrenergic agonist albuterol, we undertook a trial to evaluate the efficacy of strength training, albuterol, and the combination of

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Supported by a government grant of the Health Research and Development Council of the Netherlands (ZON-MW), the Prinses Beatrix Fonds, the Dutch Public Fund for Neuromuscular Disorders (VSN), and the Dutch FSHD Foundation.

Received November 12, 2003. Accepted in final form April 29, 2004.

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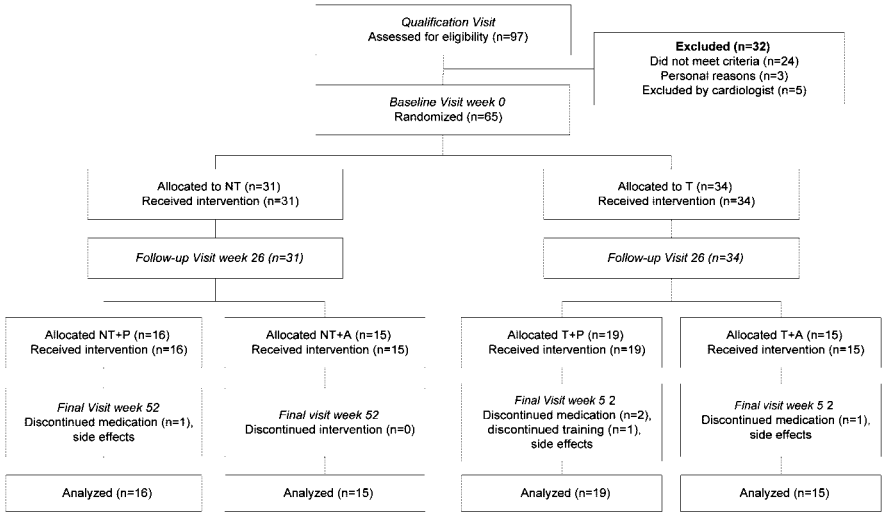

Figure 1. Study design and flow of patients through each stage of the study. NT = non-training group; T = training group; P = placebo; A = albuterol.

both interventions on skeletal muscle strength, endurance, and muscle volume in patients with FSHD.

Methods. *Subjects.* Patients with a clinical diagnosis of FSHD were recruited through The Dutch Neuromuscular Diseases Association and the Neuromuscular Center Nijmegen (The Netherlands). Their diagnosis was genetically confirmed as all included patients, or a first degree relative, had a D4Z4 deletion at 4q35 with *Eco*RI fragments smaller than 35 kb after double digestion with *Bln*I.[17]

Eligible patients were between 18 and 65 years of age, were willing to train if allocated to the training group, agreed to refrain from training if allocated to the non-training group, and agreed to use the study medication as prescribed. Patients had to have at least two trainable muscle groups (fully supinated elbow flexion Medical Research Council (MRC) ≥ 3, ankle dorsiflexor ≥ 0° dorsiflexion from neutral ankle position). Exclusion criteria were inability to walk independently (ankle-foot orthoses and canes were accepted); history of (treated) hypertension, heart failure, or ischemic heart disease, arrhythmias, diabetes mellitus, or thyrotoxicosis; use of sympathicomimetics, beta-blockers, or systemic corticosteroids during the last 3 months; (planned) pregnancy or breastfeeding; and articular diseases of the elbow or ankle joints. Patients with abnormalities on their electrocardiogram, but without a cardiovascular history or hypertension, were seen by the cardiologist to decide on their inclusion.

Design. The diagram in figure 1 shows the study design and the flow of patients through each stage of the study. After a qualification visit patients were stratified into two groups: patients with three or four trainable muscle groups (elbow flexors and ankle dorsiflexors) and patients with two trainable muscles. Patients in both strata were randomly assigned to one of the four treatment groups according to a computer generated randomization list. These treatment groups consisted of training plus albuterol, training plus placebo, non-training plus albuterol, or non-training plus placebo. Information on the assignment to training or non-training was disclosed to the patients by the physical therapist after their baseline visit. Training or non-training was the first intervention, starting just after the baseline visit until after the final visit at 52 weeks. After 26 weeks patients received the blinded trial medication dispensed by the pharmacy department. The clinical evaluator was blinded for the assignment to both interventions. The patients, physical therapist, and the neurologist evaluating the side effects were blinded for the study medication. The local ethics committee approved the study, and informed consent was obtained from all subjects.

Interventions. Strength training program. The moderate resistance strength-training program included dynamic and isometric exercises with specially developed training weights (Fysiomed, Drachten, The Netherlands) focusing on elbow flexors and ankle dorsiflexors. We decided to focus on these two muscle groups, because we wanted patients to train an upper and a lower extremity, a proximal and a distal muscle group having clear functions in daily live, and muscle groups known to be affected in various degrees in FSHD. Patients trained three non-consecutive days per week for the duration of 52 weeks, until after the final visit. The training weights were based on repetition maximum (RM) measurements. An X RM is the weight a person can lift X times—but not X + 1 times—at a steady controlled pace through the full range of joint motion.[18,19] Personal 10 RM training weights for both elbow flexors and both ankle dorsiflexors were estimated by the physical therapist. The progressive overload scheme started with a conditioning period of 8 weeks in which patients made two sets of 5 to 10 repetitions with 10 RM training weights through the full range of joint motion. Between these two sets of dynamic exercises patients performed a 30-second isometric exercise with the same training weight. Training was intensified by prescribing sets of eight repetitions with 8 RM training weights from week 9 through 17. From week 18 on patients trained with frequently adjusted 5 RM weights, making five repetitions per set.[20,21] All exercises could be executed within 30 minutes. Patients were visited at home every third week by the physical therapist to optimize the quality of performance of the exercises, to adjust the training weights, and to note possible adverse effects. The patients in the control group were instructed to continue their usual amount of physical activity during the year and not to start any type of exercise program. They were also visited by the physical therapist just before or after their study visits, to improve the compliance with these instructions, and to perform one of the strength tests (explained in Testing muscle strength and endurance).

Study medication. After 26 weeks the patients started using the β2-adrenergic agonist albuterol (sustained-release capsules, 8 mg twice daily, Hexal AG, Holzkirchen, Germany) or the indistinguishable placebo. EKGs were evaluated by the cardiologist. Before distributing the study medication serum potassium was checked, as albuterol per os can induce hypokalemia.[22] Patients started with one capsule a day for 2 weeks. After 2 weeks they were called by the neurologist to check for initial side effects. If side effects were absent or acceptable patients were instructed to take one capsule every 12 hours. Treatment was continued for 26 weeks, until after the final visit. After this visit patients were called by the neurologist to obtain information on ongoing side effects, therapy compliance, and to instruct patients to discontinue study medication after using one capsule a day for 1 week. Returned capsules were counted.

Assessments. Assessments comprised a qualification visit, a baseline visit (week 0), a follow-up (26 weeks), and a final visit (52 weeks). All study visits were 1-day visits to the Neuromuscular Center Nijmegen. The purpose of the qualification visit was to obtain demographic data, a general and FSHD related medical history, anthropometric measures (height in cm, weight in kg, diastolic and systolic blood pressure in mm Hg, resting pulse rate in bpm), and an electrocardiogram, and to verify eligibility, and familiarize patients with the muscle testing and other measurements. Baseline, follow-up, and final visits consisted of a history regarding non-treatment related changes in medical and personal

Table 1 *Patient characteristics of the four treatment groups*

	Placebo, n = 35		Albuterol, n = 30	
Characteristics	Non-training, n = 16	Training, n = 19	Non-training, n = 15	Training, n = 15
Female/male	7/9	8/11	6/9	4/11
Age, y	39 ± 9	36 ± 9	41 ± 12	36 ± 11
Length, cm	182 ± 10	180 ± 9	179 ± 8	180 ± 7
Weight, kg	78 ± 11	75 ± 12	71 ± 9	76 ± 14

Means ± 1 SD.

circumstances, anthropometrics, muscle strength testing, muscle volume testing, functional tests, timed motor performance tasks, and pulmonary function tests. All data were collected by the clinical evaluator unless otherwise specified.

Outcome measures. For the effect of training the primary outcome measure was the maximum voluntary isometric strength (MVIC)[23,24] of the elbow flexors and ankle dorsiflexors. Main secondary outcomes were muscle endurance[25] and dynamic muscle strength[18,19] of elbow flexors and ankle dorsiflexors. To evaluate the effect of albuterol the MVIC of the following individual muscle groups was used as primary outcome measure: shoulder abductors, shoulder external rotators, elbow flexors, elbow extensors, knee flexors, knee extensors, ankle dorsiflexors, and handgrip. In order to detect differential responses in separate muscle groups mean changes in strength of individual muscle groups were evaluated, instead of a change in a composite score. Secondary outcome measures were muscle endurance and the total body skeletal muscle volume estimated by stereologic CT method.[26,27] Other measures included the urinary creatinine method,[28,29] functional tests,[23] timed motor performance tasks,[23] and pulmonary function tests.[30]

Testing muscle strength and endurance. MVIC testing was performed on a Quantitative Muscle Assessment fixed myometry testing system (The Computer Source, Gainesville, GA). Handgrip was measured with a computer interfaced Jamar grip dynamometer attached to the equipment. Muscle groups were tested on both sides in a standardized way by one well-trained, blinded clinical evaluator.[23,24] The higher of two maximal isometric contractions, each of approximately 3 to 4 seconds, was used for data analysis. To measure muscle endurance patients were urged to sustain a maximal isometric contraction for 30 seconds. The area under the curve from second 5 through 30 of the force-time plot is known as the force-time integral (FTI30).[25] The dynamic strength of the trained muscles—elbow flexors and ankle dorsiflexors—was evaluated using the 1 RM, the weight a person can lift once, but not twice, at a steady controlled pace through the full range of joint motion.[18,19] The RM measurements were performed by the physical therapist, who was not blinded for the allocation to training or non-training, as this specific measurement carried too great a risk of unblinding the clinical evaluator.

Testing muscle volume. A stereologic CT quantification method based on the Cavalieri principle was used for the estimation of total human skeletal muscle volume.[26,27] The 24-hour urinary creatinine excretion (24-hour UCE) method was an additional measure for the estimation of total body skeletal muscle mass.[28] Skeletal muscle mass (in kg) was derived from the 24-hour UCE (in g) using the following prediction equation: skeletal muscle mass = 21.8 × 24-hour UCE.[29]

Functional tests and timed motor performance tasks. The functional tests consisted of the assessment of a functional upper extremity grade and functional lower extremity grade, described elsewhere.[23] The timed motor performance tasks included standing from lying supine, standing from sitting, walking 30 feet (9.14 m), and climbing three standard stairs.[23]

Pulmonary function tests. Pulmonary function tests comprised the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV1) obtained with a facemask-adjusted spirometer (Morgan, PM2000) and the maximal inspiratory mouth pressure (MIP) and maximal expiratory mouth pressure (MEP) measured with a facemask-adjusted pressure manometer (Morgan, Pmax).[30]

Statistics. Power. The study was designed to detect a relative difference between the FSHD patients after treatment with training plus albuterol, training plus placebo, non-training plus albuterol, or non-training plus placebo. Power analysis showed that 14 patients were needed in each arm of the trial (power 80%, $\alpha = 0.05$, F-test, 4-groeps). The minimum relative improvement as result of the treatment with strength training or albuterol was expected to be 7.5% (5 to 10%) with a SD of 6.5% (5 to 8%).[11,31]

Statistical analysis. Efficacy analyses were performed on an intention-to-treat basis, such that all randomized subjects were included in the analyses. A general linear mixed model was used to study possible differences among the four groups on the primary outcome measure (MVIC strength), and secondary outcome measures, separately. The fixed independent variables were the study "visit" (0, 52 weeks), "training" (yes, no), "albuterol" (yes, no), "gender" (male, female), and "severity" (≥3, 2 trainable muscle groups). Per patient a random intercept was allowed. To detect differences between visits related to any of these variables all first order interaction terms between these variables and "visit" were included. Higher order interaction terms, except one second order term (training * albuterol * visit) were excluded from the model, as they appeared to be not significant (at the level of $\alpha = 0.05$). The estimated means and effect sizes (difference in mean change from baseline analyzed by intervention over all treatment groups) with 95% CI are presented. Tukey-Kramer adjustments for multiple comparisons were performed.

Results. *Subjects and design.* In the qualification period 32 of 97 patients withdrew or were excluded from further participation because of the following reasons: cardiovascular problems or history (n = 10), not able to walk independently or less than two trainable muscle groups (n = 7), meeting other exclusion criteria (n = 7), and personal reasons (n = 3) (see figure 1). The cardiologist disapproved the use of trial medication for five patients with EKG abnormalities. Sixty-five patients were admitted to the study and randomized. The demographic characteristics are presented by treatment group in table 1. One patient stopped training because of recurring, training-related muscle soreness and fatigue. She had a second diagnostic workup, revealing a mitochondrial myopathy as well as FSHD. Four patients stopped using their study medication because of side effects. Three of them were on placebo (two combined with training, one without training), one on albuterol (combined with training). Data of the patients who discontinued an intervention were analyzed in the assigned treatment group (intention-to-treat principle).

Allocation to the training or non-training group was unmasked in three cases, due to unintentional remarks. The success of blinding for the study medication was not formally checked.

Baseline data and outcomes. Effect of strength training and albuterol on trained muscle groups. Effect of strength training and albuterol on trained muscle groups

Table 2 *Results of strength training vs non-training and albuterol vs placebo on strength of "trained" muscle groups*

	Placebo, n = 35		Albuterol, n = 30		Effect size	
Variable	NT, n = 16	T, n = 19	NT, n = 15	T, n = 15	T − NT	A − P
Elbow flexion right						
MVIC, week 0	17.3 (13.7–21.0)	12.6 (9.3–16.0)	14.0 (10.2–17.8)	15.1 (11.3–19.0)	0.6 (−0.4–1.5)	1.1 (0.2–2.0)
week 52	16.0 (12.4–19.7)	12.2 (8.8–15.5)	14.1 (10.3–17.9)	15.4 (11.6–19.3)	0.23	0.02
FTI30, week 0	281 (211–352)	221 (156–286)	259 (185–332)	241 (166–316)	2 (−18–22)	20 (0–39)
week 52	278 (207–349)	210 (145–275)	264 (191–338)	259 (185–334)	0.86	0.05
1RM, week 0	6.5 (4.8–8.2)	5.7 (4.0–7.4)	6.0 (4.1–7.9)	5.8 (3.9–7.6)	1.2 (0.2–2.1)	0.9 (−0.1–1.9)
week 52	7.5 (5.8–9.2)	7.8 (6.1–9.5)	7.8 (5.9–9.7)	8.9 (7.0–10.7)	0.02	0.06
Ankle dorsiflexion right						
MVIC, week 0	10.8 (7.8–13.9)	10.4 (7.6–13.2)	9.9 (6.7–13.1)	9.7 (6.4–12.9)	0.4 (−1.7–2.4)	0.2 (−1.8–2.3)
week 52	9.6 (6.5–12.6)	8.7 (5.9–11.5)	8.0 (4.8–11.2)	9.0 (5.8–12.3)	0.72	0.82
FTI30, week 0	189 (133–245)	205 (155–256)	195 (139–252)	181 (123–239)	−1 (−42–41)	−4 (−46–38)
week 52	160 (104–216)	159 (109–210)	144 (87–202)	149 (90–207)	0.97	0.85
1RM, week 0	5.9 (4.4–7.5)	5.4 (4.1–6.7)	5.9 (4.5–7.4)	6.2 (4.7–7.6)	−0.4 (−1.7–0.9)	0.2 (−1.1–1.5)
week 52	4.7 (3.2–6.2)	3.9 (2.6–5.2)	5.1 (3.7–6.5)	4.6 (3.2–6.1)	0.50	0.81

Mean values (95% CI) for all strength modalities of the right-sided "trained" muscle groups at the baseline (week 0) and final visit (week 52) presented by treatment group (i.e., non-training and placebo, training and placebo, non-training and albuterol, training and albuterol). As no significant interactions between the two interventions (i.e., training vs non-training; albuterol vs placebo) could be detected, the effect sizes are presented by intervention. The effect sizes (95% CI; p value) represent the difference in mean change from baseline, analyzed by intervention (i.e., training vs non-training; albuterol vs placebo) over all treatment groups. Changes in strength measures for the left-sided trained muscle groups were not essentially different. MVIC expressed in kgF, FTI30 in kgF·s, and 1RM in kg.

NT = non-training group; T = training group; A = albuterol; P = placebo; MVIC = maximum voluntary isometric strength; FTI = force-time integral; RM = repetition maximum.

is illustrated in table 2. After 52 weeks the elbow flexors did not differ significantly between the training and non-training group for isometric strength (MVIC, the primary outcome measure) and isometric endurance (FTI30). Dynamic strength, as measured by the 1 RM, showed a larger increase in the training group compared to the non-training group (effect size right side 1.2 kg, CI 0.2 to 2.1, $p = 0.02$; left side 1.5 kg, CI 0.6 to 2.4, $p = 0.002$). The MVIC strength of the elbow flexors increased in the albuterol-treated patients, while we observed a decline in the placebo group (effect size right side 1.1 kgF, CI 0.2 to 2.0, $p = 0.02$; left side 1.2 kgF, CI 0.3 to 2.1, $p = 0.01$). At 52 weeks the differences in changes from baseline for elbow flexors endurance (FTI30) and dynamic strength (1 RM) between the albuterol and placebo group were not significant. The strength measures of the ankle dorsiflexors in all four groups decreased significantly and markedly. This decrease was not influenced by training or the use of albuterol. The clinical evaluator, the physical therapist, and some of the patients were clinically aware of the worsening function of the ankle dorsiflexors. When training and albuterol were combined, neither synergistic nor antagonistic effects could be detected for the elbow flexors or for the ankle dorsiflexors. Changes in strength measures for the left-sided trained muscle groups did not essentially differ from the right-sided.

Effect of albuterol on non-trained muscle groups, muscle volume, and other outcomes. Data are presented in table E-1 (available on the *Neurology* Web site; go to www.neurology.org) and figures 2 and 3. Whereas in the placebo group 10 non-trained muscle groups showed a small to moderate decline in mean MVIC strength, in the albuterol-treated patients four muscle groups demonstrated a small decrease, three showed no change, and five a small increase in MVIC strength. The favorable differences in changes from baseline for the albuterol group as compared to the placebo group reached significance ($p < 0.05$) in 7 out of 12 muscle groups. The baseline values and changes for endurance (FTI30) nearly matched the data on MVIC strength, although the differences between groups only attained significance ($p < 0.05$) in 4 out of 10 muscle groups (knee flexors were not retested due to frequent cramps).

The gain in muscle volume, estimated by stereologic CT method, in the albuterol group vs the small loss in the placebo group (see figure 3) was significant (1.5 l, CI 0.5 to 2.4, $p = 0.003$), and paralleled the changes observed with the 24-hour UCE method (2.5 kg, CI −0.1 to 5.2, $p = 0.060$).

Anthropometric measures, functional tests, timed motor performance tasks, and pulmonary function tests did not demonstrate relevant changes, except for the pulse rate. In the placebo group the mean resting pulse rate remained stable, whereas the mean resting pulse rate in the albuterol group rose significantly (effect size 10.2 bpm, CI 6.5 to 14.0, $p < 0.0001$).

Tolerability. The training program was well tolerated. Patients experienced no notable general fatigue or muscle soreness. The training-induced muscle fatigue lasted less than an hour, so daily activities could be carried out normally afterwards. Eleven out of 34 patients in the training group reported pain in neck and shoulder region to the physical therapist during his home visits. Five mentioned

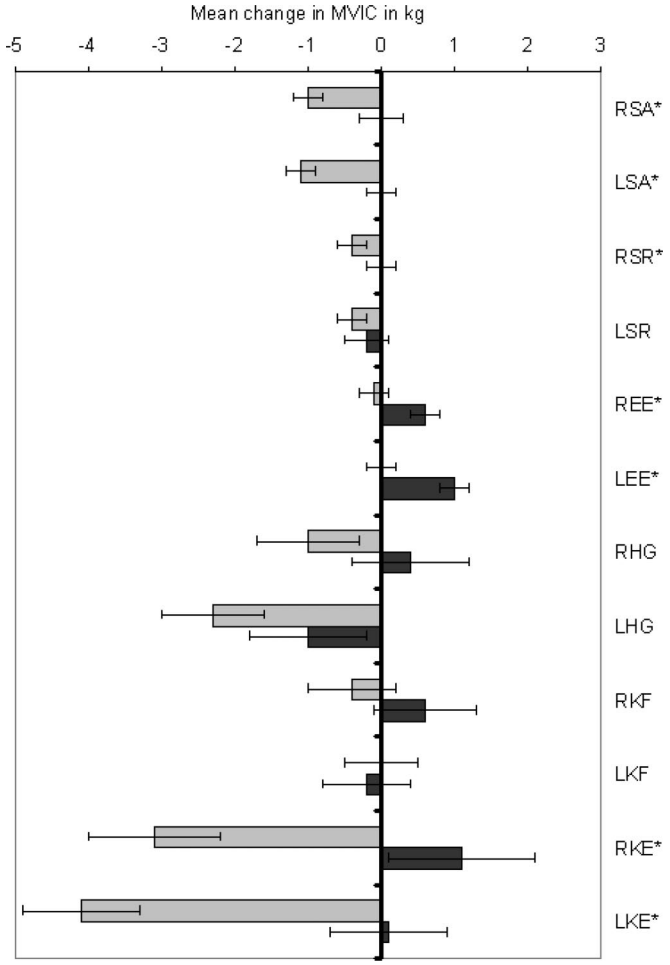

Figure 2. Mean changes from baseline for maximum voluntary isometric strength for the individual non-trained muscle groups for the placebo (light gray bars) and albuterol groups (dark gray bars). Error bars represent ± 1 standard error. Asterisks indicate p *values < 0.05 for differences in changes from baseline between the placebo and albuterol groups. R = right; L = left; SA = shoulder abductors; SR = shoulder external rotators; EE = elbow extensors; HG = handgrip; KF = knee flexors; KE = knee extensors.*

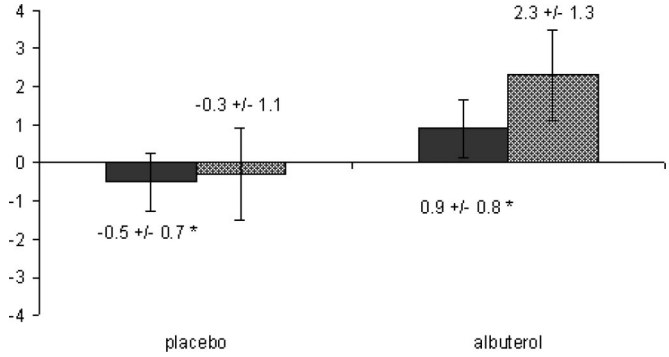

Figure 3. Mean changes from baseline for total skeletal muscle volume in L (dark gray bars) estimated using the stereologic CT method, and muscle mass in kg (dotted gray bars) estimated using the 24-hour UCE method, for the placebo and albuterol groups. Error bars represent ± 1 standard error. Asterisks indicate p *values < 0.05 for differences in changes from baseline between the placebo and albuterol groups.*

a period with elbow complaints. The number of neck-shoulder and elbow complaints did not differ between groups at baseline and at the final visit (table 3).

Ten patients reported tremors in the week they started using albuterol. Placebo-treated patients mentioned no tremors. Other reported adverse effects of study medication are listed in table 4.

Discussion. We evaluated the efficacy of strength training and albuterol on skeletal muscle strength, endurance, and volume in patients with FSHD. We combined these interventions as we expected an additive effect of training on the effects of albuterol.

In our study moderate resistance exercises of elbow flexors did not change the primary outcome—MVIC strength at 52 weeks. The dynamic strength of the elbow flexors improved markedly. Exercising the ankle dorsiflexors did not influence the substantial loss in all strength modalities as observed in the control group, nor did the use of albuterol (see table 2). Albuterol had a small positive effect on MVIC strength (primary outcome measure) and endurance in most assessed non-trained muscle groups, and on muscle volume and mass as well (table E-1, available online at www.neurology.org; see figures 2 and 3). Contrary to our expectation no synergistic effects between training and albuterol were detected; also no antagonistic effect was observed. Both interventions were well tolerated (see tables 3 and 4).

The positive effect of strength training on the dynamic strength (1 RM) of the elbow flexors confirms the moderate positive effect of strengthening exercises as reported in previous studies.[6-9] However, the strength training program did not have a positive effect on isometric strength (MVIC, primary outcome) and isometric endurance. The positive response of the dynamic strength in the absence of a gain in isometric strength is most likely due to the specificity of the training. This means that a training program with dynamic exercises increases dynamic strength more than isometric strength, and vice versa.[32,33] The observed absence of a concomitant increase in isometric strength could also reflect a diminished ability of the diseased neuromuscular system to carry over effects of a specific training

Table 3 *Neck, shoulder, and elbow complaints*

	Non-training, n = 31		Training, n = 34	
Symptoms	Week 0	Week 52	Week 0	Week 52
Pain neck–shoulder	22/31	17/31	21/34	19/34
Pain elbow	2/31	1/31	3/34	2/34

Number of patients reporting neck, shoulder, and elbow complaints in the training and non-training group at the baseline visit (week 0) and final visit (week 52).

Table 4 *Adverse effects of study medication*

Symptoms	Placebo, n = 35		Albuterol, n = 30	
	Week 26 + 1	Week 52 + 1	Week 26 + 1	Week 52 + 1
Tremors	0	0	10	0
Muscle cramps	0	1	3	1
Headache	3	0	3	0
Nausea	2	0	3	0
Nervousness	2	0	2	0
Tachycardia/palpitations	4	2	2	1
Skin problems	2	2	0	0
Hot flushes	1	0	2	0
Others-atypical	3	1	7	6
One or more symptoms	15	5	17	3

Number of patients reporting adverse effects of study medication 1 week after starting study medication (week 26 + 1) and 1 week after the final visit (week 52 + 1).

program from one strength modality to another. This cannot be proven, or excluded, as the size of the carryover effect cannot be predicted.[34] In practice, the specificity of training means that what you train is what you get. So, isolated resistance exercises are of limited use, when the objective is to benefit on a functional level (e.g., walking).

In contrast to the elbow flexors, strength of the ankle dorsiflexors (isometric and dynamic) was not influenced by training. A difference in grade of muscle weakness at baseline between elbow and ankle dorsiflexors might hold the explanation for the difference in their response to training. In our study elbow flexors were eligible for MVIC muscle testing and training when MRC was ≥ 3, ankle dorsiflexor when $\geq 0°$ dorsiflexion from neutral ankle position was possible, which corresponds to a MRC < 3. So, pre-exercise weakness might have been more severe in ankle dorsiflexors compared to elbow flexors. In neuromuscular patients absolute gain in muscle strength consequent to strength training is probably related to pre-exercise muscle strength, and severely weak muscles (<10% of normal strength) in general may not improve.[8] Differences in genetic make-up, histologic and biochemical composition, biomechanical function, and level of daily muscular activity between elbow flexors and ankle dorsiflexors muscles might contribute to the different outcome as well.

It is of clinical importance that our findings do not support the hypothesis of extra risk for muscle strain in FSHD patients.[4,5] It should be taken into account that all strength training studies, including the present one, impose only a controlled strain for a relatively short period. More chronic exertion may have an undetermined effect on disease progression.

After the open-label pilot trial in 15 FSHD patients the FSH-DY group reported a significant increase in muscle strength and mass when given albuterol (SR, 16.0 mg/day) for 3 months.[11] In the subsequent randomized, double-blind, placebo-controlled trial no improvement of strength, expressed as a composite MVIC score derived from the MVIC values of multiple muscle groups, could be detected after 1 year of treatment.[12] The positive effect on some secondary outcomes (strength measures and lean body mass) after 1 year led to the hypothesis that the anabolic effects of albuterol probably wear off with prolonged use, due to downregulation of β2-receptors. The improvement in muscle strength and muscle mass after 6 months of exposure to albuterol in our study confirms the short term anabolic effect, but does not preclude a long-term effect.

The FSH-DY group postulated another explanation for the inability to reproduce the positive effect of their pilot trial, namely a differential expression in β2-receptors in proximal and distal muscle groups, combined with an overrepresentation of proximal muscle groups in the composite MVIC strength score. This explanation was based on the significant gain in grip strength observed in their albuterol treated patients. Our data support a differential response of different muscle groups in natural course and in effect of albuterol (and training). However, in our study the assessed distal muscle groups, hand muscles and ankle dorsiflexors, failed to show a positive effect of albuterol.

In rats, the β2-adrenergic agonist clenbuterol does have muscle-specific anabolic effects, but this muscle specificity cannot be reliably predicted by fiber-type composition and β2-receptor density.[16] Too little is known about the distribution of fiber-types and β2-receptors in different muscle groups of healthy individuals and patients with FSHD to suggest a hypothesis on their role in the differences in response of different muscle groups.[1,35,36] The response of individual muscles to albuterol is more likely caused by multiple interacting factors, such as differences in genetic and biochemical make-up, histologic composition, biomechanical function, and disease severity, than by fiber-type composition and density of β2-receptors alone.

Several issues regarding the design and results of this study must be addressed. First, considering the specificity of training, one might argue we should have taken the dynamic 1 RM measure as primary outcome to evaluate our mainly dynamic exercise program, or should have chosen an isometric training regimen. There were two reasons not to take the 1 RM as primary outcome measure: it was performed by the unblinded physical therapist for it carried to great a risk to unblind the clinical evaluator, and we wanted to have one uniform outcome measure for both interventions. An isometric training has too many practical limitations to be performed at home. Moreover, dynamic resistance exercises are preferable as they mimic everyday activities best.[20] Second, the dynamic strength (1 RM) of elbow flexors increased significantly, not only in the training, but also in the non-training group. A possible explana-

tion could be a systematic error due to or systematic change in the performance of the elbow flexor dynamic strength measurement. A test-retest learning effect is a less likely explanation, as the period between tests was 6 months. Third, additional analyses on the relation between pre-exercise severity of weakness and effect of training and albuterol were not performed, for this was not a prespecified objective of our study. Taking into account the small effects of the interventions, additional analyses did not seem appropriate.

On the basis of our experience in this trial we tell our FSHD patients that normal participation in sports and work appears not to harm their muscles, and may help maintain their cardiorespiratory fitness. On the other hand, there is insufficient ground for general prescription of exercise programs in FSHD. When asked for training advice, our current recommendation is to train under supervision of a specialized therapist to monitor (side) effects and prevent injuries, and to combine strength training with more functional exercises to facilitate generalization of the training effects to daily life activities.[37]

In FSHD albuterol (SR capsules, 8 mg twice daily) is a very well tolerated anabolic aid, but consequences of prolonged use and the effect on disabilities and quality of life are presently unclear and therefore preclude routine prescription. Periodic use of albuterol might prevent a wearing off of the anabolic effect. Exploring the efficacy of alternative dosing regimens, whether or not in combination with other ergogenic medication, is required. The differential response of different muscle groups to albuterol could be studied in a meta-analysis.

Acknowledgment

The authors thank W.M. King for training the clinical evaluator; J.T. Kissel, J.R. Mendell, and R. Tawil for advice; and Hexal AG, Holzkirchen, Germany, for providing the study medication.

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